



**North America, Inc.
Radiesse® Dermal Filler**

**“Radiesse® PostApprovalSafetyStudy For the
Treatment of Hands With Moderate to Very Severe
Dorsal Volume Loss”**

**NCT02904096, redacted
version v1.0, 18Nov2019**

STATISTICAL ANALYSIS PLAN VER. 2.0

PROTOCOL NUMBER: P151009

PREPARED BY: [REDACTED]

SPONSOR:

**Merz North America, Inc.
6501 Six Forks Road
Raleigh, North Carolina 27615**

DATE: FEB 12, 2019

CAUTION - Investigational device. Limited by United States law to investigational use.

This document contains information that is confidential and proprietary. The contents of this document may not be copied without written permission from the Sponsor.

SIGNATURE PAGE

"Radiesse® PostApproval Safety Study For the Treatment of Hands With Moderate to Very Severe Dorsal Volume Loss"

STATISTICAL ANALYSIS PLAN VER. 2.0

PROTOCOL NUMBER: P151009

PREPARED BY: [REDACTED]

SPONSOR:

Merz North America, Inc.
6501 Six Forks Road
Raleigh, North Carolina 27615

DATE: FEB. 12, 2019

Approvals:

[REDACTED]

[REDACTED] Merz Pharmaceuticals Date
GmbH, Senior Biostatistician

12-Feb-2019

[REDACTED]

Date: 2019.02.13 11:06:26 -08'00'

[REDACTED]

Date

Principal Product Development Strategist

Table of Contents

1.	Introduction	1
2.	Study Design.....	1
3.	Sample Size Estimation	1
4.	Randomization and Blinding	2
4.1.	Randomization	2
4.2.	Blinding	2
5.	Analysis Populations	2
5.1.	Safety Evaluation Set (SES).....	2
5.2.	Per Protocol Set (PPS)	2
6.	Study Endpoints	3
6.1.	Primary Safety.....	3
6.2.	Secondary Safety.....	3
	
6.4.	Secondary Effectiveness	3
	
7.	Analysis	4
7.1.	Primary Safety Endpoint	4
7.2.	Secondary Safety Endpoints	4
	
7.4.	Additional Safety Analyses.....	5
7.5.	Secondary Effectiveness Endpoints	7
7.6.	Subject Accountability	8
7.7.	Demographics	8
7.8.	Concomitant Medication	8
7.9.	Extent of Exposure	8
7.10.	Protocol Deviations.....	8
7.11.	Subgroup Analyses.....	8
7.12.	Handling of Missing Data	9
8.	Changes in Analyses Described in the Protocol	9
9.	References	10
9.1.	Appendix 1: List of Tables, Figures, Listings.....	10

1. Introduction

This study, a post approval study (PAS), is being conducted to satisfy a condition of the June 4, 2015, PMA-S (P050052/S049) approval of Radiesse® injectable implant indicated for hand augmentation to correct volume loss in the dorsum of the hand. This study will provide safety and effectiveness data in subjects with more severe volume loss than those subjects evaluated in the pre-market study. The pre-market (Merz protocol #P110607) study cohort excluded subjects with baseline grade 4 hands.

Radiesse® dermal filler was demonstrated to be safe and effective in the pre-market study for treatment of hands with moderate to severe dorsal volume loss. On the validated Merz Hand Grading Scale (MHGS), these were hands rated as grade 2 or grade 3 at baseline, or before treatment. With the Food and Drug Administration (FDA) approval of Radiesse® for treatment of these hands, it is anticipated that patients with MHGS grade 4 hands will seek treatment. Subjects will receive an initial Radiesse® hand treatment and have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up.

2. Study Design

This is a prospective, open-label 2 year post approval study in up to 250 subjects to evaluate the safety and effectiveness of Radiesse® implantation for very severe volume loss in the dorsum of the hands in MHGS grade 4 subjects. Two groups will be enrolled with approximately 125 subjects in each group. Group A will consist of subjects with baseline MHGS grade 4 hands and Group B will consist of subjects with baseline MHGS grade 2 or grade 3. These subjects will be followed for two years with follow-up visits at 2 weeks, and at 1, 3, 6, 12, 18, and 24 months. At 6, 12, and 18 months, all subjects will be given the option of having a re-treatment. For those receiving re-treatment, an additional 72 hr follow-up telephone call will be made as well as a one month post re-treatment office visit. This results in the potential to have 7, 13, and 19 month follow-up data.

The primary safety endpoint will be evaluated at the 6 month time point comparing Group A with Group B.

3. Sample Size Estimation

Analysis of the primary safety endpoint will be based on a non-inferiority hypothesis test comparing the 6- month rate of device/injection-related severe AEs in the MHGS grade 4 subjects (Group A) versus the MHGS grade 2 and grade 3 subjects (Group B). Based on the pre-market study data, an expected rate of severe adverse events is 17% for both groups, and the test will be based on a 12% non-inferiority margin. This margin allows for adequate power of the planned hypothesis test with a reasonable sample size and will provide

assurance that the severe AE rate in the MHGS grade 4 subjects is not unacceptably higher given the expected benefit in these subjects. The test will be based on a one-sided Farrington-Manning likelihood score test of binomial proportions at a one-sided 0.05 alpha level. A maximum of 250 subjects with MHGS grades 2, 3 and 4 at baseline (at least 50% with both hands rated MHGS 4) will be enrolled in at least 5 sites and a maximum of 12 sites in the US. Allowing for some attrition, a total of 244 subjects (122 in each group) at 6 months will provide approximately 80% power to conduct the hypothesis test. Based on an expected attrition rate of 5% per year, a minimum of 225 evaluable subjects are required to provide 2-year follow-up data.

4. Randomization and Blinding

4.1. Randomization

This study is not randomized. Subjects are enrolled directly into Groups A or B based on their baseline MHGS grade and are all treated with Radiesse®.

4.2. Blinding

This is an open label study and as such subjects and treating physicians are not blinded. However the site evaluator will be blinded in the sense that he/she will not have access to previous ratings for subjects participating in the study and will also be blinded as to whether or not a subject has had repeat treatment(s). To ensure that the blind is maintained, subjects will have their upper body and face hidden behind a barrier screen with only their hand visible to the masked evaluator. Subjects will be asked to remain silent during the MHGS evaluation process. Masked evaluators will not be allowed to discuss treatment schedules with treatment investigators and study staff at the site, and will not enter data on case report forms that contain information that would break the blind.

5. Analysis Populations

5.1. Safety Evaluation Set (SES)

The SES is the subset of all subjects who were exposed to study device at enrollment.

5.2. Per Protocol Set (PPS)

The PPS is the subset of subjects in the SES without major protocol deviations. Examples of a major protocol deviation would be absence of Radiesse® hand

treatment or receiving an exclusionary hand procedure during the study. Major protocol deviations will be determined at a data review meeting prior to database lock.

6. Study Endpoints

6.1.Primary Safety

6-month rate of device/injection-related severe adverse events.

6.2.Secondary Safety

24 month rate of device/injection-related severe AEs.

Hand function testing at baseline, study exit, and other collected time points.

[REDACTED]

[REDACTED]

[REDACTED]

6.4.Secondary Effectiveness

MHGS at 3-months after initial treatment

MHGS at 3-months following retreatment for those receiving retreatment.

GAIS at 3-months after initial treatment.

GAIS at 3-months following retreatment for those receiving retreatment.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



7. Analysis

All endpoints will be analyzed using the SES population.

If the PPS differs from the SES, the analysis of the primary safety endpoint (including that by subgroups) will be performed on the PPS, too, for sensitivity. The enrollment table as well as the table on demographics will be repeated for the PPS (for description of this population).

7.1. Primary Safety Endpoint

The primary safety endpoint analysis will be based on a non-inferiority hypothesis test. Stated in terms of the null and alternate hypothesis, this is as follows:

H_0 (null): $P_A - P_B \geq 12\%$ vs

H_a (alternate): $P_A - P_B < 12\%$

Where P_A and P_B are the percentages of subjects in Groups A and B who experience a device/injection-related severe adverse event by 6 months. Percentages will be calculated using the number of subjects experiencing at least one device/injection related severe treatment emergent adverse event (TEAE) by six months post-treatment as the numerator divided by the number of subjects in the SES (PPS) population with six month follow-up data.

TEAEs are defined as adverse events with onset or worsening after the first injection of Radiesse.

The test will be based on the Farrington-Manning likelihood score test. Testing will be done by constructing a one-sided 95% confidence interval using the Farrington-Manning method. If the upper 95% confidence bound around $P_A - P_B$ is less than 12%, H_0 will be rejected in favor of H_a , thus demonstrating non-inferiority, otherwise the H_0 will be accepted.

7.2. Secondary Safety Endpoints

The number and percentage of subjects with at least one device/injection-related severe TEAE within 24 months of initial treatment as well as the number of events will be presented by group and in total. Percentages will be calculated using the number of subjects experiencing at least one device/injection related severe TEAE by 24 months

post-treatment as the numerator divided by the number of subjects in the SES population with 24 month follow-up data. The difference between the two proportions of subjects in groups A and B is calculated and presented together with a one-sided exploratory 95%-CI constructed via the Farrington-Manning likelihood method. No formal hypothesis testing will be done for this endpoint.

Hand-function data will be summarized descriptively and compared to baseline. Hand-function data were evaluated in relation to the incidence of a significant MHQ change or report(s) of severe difficulty performing activities with the hand(s) or severe loss of sensation in the hand(s) since previous visit. Correlation will be plotted between two hand-function test investigators for the first 10 subjects enrolled at each site. Differences between sites in hand-function results will be summarized descriptively and compared to baseline.

[REDACTED]

[REDACTED]

[REDACTED]

7.4. Additional Safety Analyses

[REDACTED]

The number and percentage of subjects experiencing physician reported TEAEs as well as the number of events itself will be reported for the following time periods:

- following initial treatment but occurring before retreatment,
- following month 6 retreatment but occurring before further retreatment,

- following month 12 retreatment but occurring before further retreatment,
- following month 18 retreatment but occurring before further retreatment.

The same will be done for subject-reported TEAEs.

Further, both, physician- and subject-reported TEAEs, will be analysed by maximum severity, by maximum duration and by number of treatments. Physician-reported TEAEs will additionally be analysed by maximum relationship.

In case of missing diary entries, the duration of a subject-reported TEAE will be calculated as follows:

- a. ***If the subject misses ONE day of diary entry, it is assumed that they had the event during that day they “forgot” . The event will be counted as one TEAE then.***
 - i. *Example= Bruising reported on days 1, 2, 4, 5 and no diary entry on day 3; this would be a 5 day bruise of one TEAE*
 - ii. *Example= Swelling reported on days 2, 4, 5, 7 and no diary entry on day 3 or 6; this would be a 6 day swelling of one TEAE*
- b. ***If the subject misses TWO OR MORE days of diary entry, it is assumed that they did NOT have the event during the 2 days they “forgot,” and **two unique TEAEs will be counted.*****
 - i. *Example= Swelling reported on days 2, 3, 6, 7, 8 and no diary entry on days 4 and 5; this would be one TEAE of swelling lasting 2 days and one TEAE of swelling lasting 3 days (two unique subject-reported TEAEs)*
 - ii. *Example= Redness reported on days 1, 2, 3, 4, 7,8 and no diary entry on days 5 and 6; this would be one TEAE of redness lasting 4 days and one TEAE of redness lasting 2 days (two unique subject-reported TEAEs)*

Differences between percentages of subjects with physician reported TEAEs in groups A and B will be presented together with exploratory 95% confidence intervals. The same will be done for subject-reported adverse events.

In addition, the number and percentage of subjects experiencing serious physician reported TEAEs as well as the number of events itself will be reported.

Kaplan-Meier time to event analyses will be performed for physician-reported adverse events.

The number and percentage of subjects with at least one device/injection-related severe TEAE over the course of the study as well as the number of events will be presented by group and in total. Percentages will be calculated using the number of subjects experiencing at least one device/injection related severe TEAE over the course of the study as the numerator divided by the number of subjects in the SES population. The difference between the two proportions of subjects in groups A and B

is calculated and presented together with a one-sided exploratory 95%-CI constructed via the Farrington-Manning likelihood method. In addition, a Kaplan-Meier time to event analysis will be performed. For subjects experiencing multiple events, the time to the first event will be used in this analysis. Subjects who do not experience a device/injection related severe adverse event until their 24 month visit will be censored at their 24 month follow-up time. Subjects withdrawing or lost to follow-up prior to their 24 month visit who have not experienced an event will be censored at their time of withdrawal or time of last known follow-up visit.

7.5. Secondary [REDACTED] Endpoints

The effectiveness endpoints „MHGS at [REDACTED] 3-[REDACTED] months after initial treatment“ will be analysed by showing summary statistics for the MHGS values and its changes from baseline at these timepoints. In addition, the numbers and percentages of subjects with at least 1 point improvement in both hands, with at least 1 point improvement in the left hand, and with 1 point improvement in the right hand will be shown together with exploratory two-sided 95% CIs for the percentages (Wilson’s score method).

[REDACTED]

The effectiveness endpoints „MHGS at 3 [REDACTED] months following retreatment“ will not be analysed. „MHGS at 3-months following retreatment“ cannot be analysed as these data were not collected during the study (there were no Month 9, Month 15 nor Month 21 visits planned). [REDACTED]

[REDACTED]

The effectiveness endpoints „GAIS at [REDACTED] [REDACTED] months after initial treatment“ will be analysed by showing summary statistics for the GAIS values at these timepoints. In addition, the numbers and percentages of subjects with improvement (i.e. with ratings of „Improved“, „Much Improved“ or „Very much Improved“) in both hands, with improvement in the left hand, and with improvement in the right hand, will be shown together with exploratory two-sided 95% CIs for the percentages (Wilson’s score method).

The effectiveness endpoints „GAIS at 3- [REDACTED] -months following retreatment“ will not be analysed. „GAIS at 3-months following retreatment“ cannot be analysed as these data were not collected during the study (there were no Month 9, Month 15 nor Month 21 visits planned). [REDACTED]

[REDACTED]

7.6. Subject Accountability

A table depicting the flow of subjects through the course of the study will be provided. This will include how many subjects dropped out and when they dropped out.

7.7. Demographics

Demographic data and other baseline characteristics will be analysed using standard descriptive methods, by group as well as in total.

7.8. Concomitant Medication

Concomitant medications will be coded according to the WHO Drug Dictionary and the number and percentage of subjects with concomitant medication will be presented by ATC level as well as by ATC level 2 and 3.

7.9. Extent of Exposure

The number and schemes of (re-)treatments and the injected volume will be analyzed using standard descriptive methods.

7.10. Protocol Deviations

All protocol deviations will be listed. The listing will be grouped by the interval in which the deviation occurred and the type of deviation.

7.11. Subgroup Analyses

Subgroup analyses will be performed for the primary safety endpoint and for the secondary efficacy endpoint “MHGS improvement at 3-month after initial treatment”. Outcomes by MHGS group (A versus B) were analyzed further by age (< 60 years versus

≥ 60 years), by Fitzpatrick skin type (Grades I, II, and III versus Grades IV, V, or VI), by initial volumes, and by study site. In these analyses, subjects were dichotomized based on injection volume less than, or greater than, or equal to the median injection volume. In the MHGS “response per hand” subgroup analysis, this was done by hand (initial total injection volume per hand), and in the MHGS “response in both hands” subgroup analysis as well as in the primary safety endpoint subgroup analysis this was done by subject (initial total injection volume by subject).

7.12. Handling of Missing Data

In the MHGS 1-point improvement analyses, treated/retreated subjects with missing MHGS values at treatment/retreatment and/or post-treatment observation visits will be counted as non-responder.

In the GAIS improvement analyses, treated/retreated subjects with missing GAIS values at any post-treatment observation visit will be counted as non-responder.

All other analyses will be based on observed data only.

8. Changes in Analyses Described in the Protocol

The following changes compared to clinical study protocol version 0.5, dated 18-SEP-2017, have been implemented in this SAP:

The secondary effectiveness endpoints “MHGS at 3-months following retreatment for those receiving retreatment” and “GAIS at 3-months following retreatment for those receiving retreatment” cannot be analyzed as these data were not collected during the study (i.e., no Month 9, Month 15, or Month 21 visits were planned).

The effectiveness endpoints „MHGS (GAIS) at 3-[REDACTED]-months following retreatment“ will not be analysed. „MHGS (GAIS) at 3-months following retreatment“ cannot be analysed as these data were not collected during the study (there were no Month 9, Month 15 nor Month 21 visits planned). [REDACTED]

The protocol indicated that repeat injection volumes would be used as a predictor for the sub-group analyses on the primary safety endpoint and secondary efficacy endpoint „MHGS at 3-months after initial treatment“. However, repeat injection occurs after both the primary safety and this secondary efficacy endpoint are measured and therefore repeat injection volume was removed as a possible predictor. In addition, the predictor „by site by

injection volume“ was reduced to „by site“ to still have reasonable number of subjects per subgroup level.

The protocol stated that repeated measures models may be explored for event data as well as for continuous data to characterize time trends. However, as there was treatment with Radiesse only and no control treatment, no time*treatment interactions could be build. Repeated measures analyses have therefore been omitted.

Similarly, the logistic regression models for the primary endpoint described in the protocol, have not been performed due to missing control treatment.

The protocol stated in section 9.2 that visits are scheduled for a specific number of days after enrollment. However, the visits are scheduled related to treatment and not related to enrollment.

9. References

1. Farrington, C. P. and Manning, G. (1990). Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk. *Statistics in Medicine*, **9**, 1447-1454.
2. Wilson, E.B. (1927). Probable inference, the law of succession, and statistical inference. *Journal of the American Statistical Association*, **22**, 209–212.

9.1. Appendix 1: Mock shells for Tables, Figures, Listings