North America, Inc.
Radiesse® Dermal Filler

"RADIESSE® POST APPROVAL SAFETY STUDY - RADIOLOGICAL EVALUATION OF IMPLANTATION IN THE HANDS"

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STATISTICAL ANALYSIS PLAN VER. 1.0
PROTOCOL NUMBER: P151010
PREPARED BY: [redacted]
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DATE: APRIL 14, 2017

SIGNATURE PAGE

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Approvals:

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Biostatistician — **Date**

[redacted] — 01 May 2017
Sr. Medical Research Scientist — **Date**

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1. Introduction

Radiesse® dermal filler is radiopaque and shows no overt radiographic safety concerns in a study of 58 patients after facial implantation, with Radiesse® not always visible on plain X-rays. This PAS study will evaluate if there are concerns after Radiesse® implantation in the dorsum of hands, specifically if implantation interferes with radiological assessment by obscuring the bones of the hand.

This clinical study is a post approval study (PAS) 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. The purpose of the PAS is to provide a radiological evaluation of hands after implantation with Radiesse®. X-rays of the hands were not taken in the pre-market study (Merz protocol #P110607) of 113 subjects.

This SAP should be read in conjunction with the study protocol and case report forms (CRFs). This version of the plan has been developed with respect to the Radiesse® Post Approval Safety Study – Radiological Evaluation of Implantation in the Hands, dated 28-Aug-2015. Any further changes to the protocol or CRFs may necessitate updates to the SAP.

2. Study Design

This is a prospective, open-label 2 year PAS evaluating radiographic appearance of Radiesse® implantation in the dorsum of the hands in 20 subjects (40 hands). All subjects will be new subjects who did not participate in the pre-market Radiesse® hand treatment study (Merz #P110607). Subjects will be consented at 1 investigational site in the United States.

For a greater understanding of potential radiographic concerns, this study will assess the effect of Radiesse® volume over time. Enrolled subjects will have baseline dorsal hand grades ranging from moderate (MHGS grade 2) to very severe volume loss (MHGS grade 4). From this, two groups will be formed. Those subjects with very severe volume loss (MHGS grade 4) will be designated as Group A while those subjects with moderate to severe volume loss (MHGS grades 2 and 3) will form Group B. The volume of Radiesse® required to correct the baseline hand condition will be lower for moderate volume loss and higher for very severe volume loss. Baseline X-rays will be taken before, and at 1-and 6-months after treatment on all subjects. If bones are not visible on the 6-month X-rays, another set of X-rays will be taken at 12-months. In the clinical practice of dermal filler implantation,

patients seek repeat treatments to sustain the aesthetic benefits. In this study, there will be the opportunity for each subject to have up to 3 repeat treatments during participation in the 24-month study. To evaluate potential radiographic safety concerns of cumulative volumes of repeat treatments over time, X-rays of the hands will be taken at 24-months on all subjects who receive 4 treatments in this study: initial treatment plus 3 repeat treatments.

Multiple assessments will be performed at each study visit. Some of the main assessments include:

- X-rays – X-rays will be taken at a licensed radiographic imaging center and transmitted to the imaging core lab to be assessed by two blinded, licensed radiologists

- MHGS – a single blinded site evaluator will grade the hands using the Merz Hand Grading System

- MHQ – subjects will self-report assessment of the effect(s) of Radiesse® injection on hand function using the Michigan Hand Outcomes Questionnaire.

- [redacted]

- GAIS – subjects will rate the aesthetically pleasing aspect of the Radiesse® hand treatment using the Global Aesthetic Improvement Scale

- AE Subject Diary – subjects use this to collect any AEs for 30 days post injection

- Photographs – at baseline and exit from the study, and during the study to document a serious or medically concerning adverse event in the hands.

Study visits

Subjects will be required to present for a total of up to 15 visits and 4 follow up phone calls. Of these visits, 7 to 10 are in-office investigational site visits and an additional 3 to 5 are X-ray visits at a licensed radiology center, and 1 to 4 are follow-up phone calls during their 24-month study participation.

If a subject only receives the initial treatment at enrollment, there will be a total of 7 in-office clinic visits, 3 x-ray visits and 1 follow-up phone call. For each of the 3 optional

repeat treatments received, there will be an additional follow-up phone call (72 hours post injection). The fourth x-ray visit will only be required at Month 12 if no bones are visible at the 6 month x-ray and the fifth x-ray visit will only be conducted if a subject receives four total treatments of Radiesse® in this PAS study.

Following consent and enrollment at the site, subjects will have X-rays taken of their hands at the radiology imaging center. Each digital radiographic image taken in the study will be assessed by 2 independent blinded, licensed radiologists at the radiology core lab. After X-rays, all subjects will return to the study clinic to receive Radiesse® treatment.

At 1-month, all subjects will have X-rays of their hands taken and will be assessed by the treating investigator for AEs.

At 6-months after enrollment, all subjects will have X-rays of their hands taken prior to receiving a repeat Radiesse® treatment, if Radiesse® retreatment is agreed upon by treating investigator and subject.

Subjects will have X-rays of their hands at 12-months only if bones of the hands were reported to be obscured by Radiesse® by at least 1 radiologist on the 6-month X-rays, and will be assessed by the treating investigator for AEs. Subjects will receive repeat Radiesse treatments at 12- and 18-month follow-up visits if Radiesse® retreatment is agreed upon by treating investigator and subject. If X-rays of the hands are required at 12 months, they will be taken prior to Radiesse® retreatment.

Subjects will have X-rays at 24-months only if they receive 4 Radiesse® treatments in the study; at enrollment, 6-, 12-, and 18-months after enrollment.

An additional 1-month follow-up visit and 72-hour follow-up phone call will be scheduled after each repeat treatment received at the 6-, 12-, and 18-month visits which would be at 7-, 13-, and 19-months, respectively.

End of study

The end of study will be defined as completion of all study visits by all enrolled subjects during the 24-month participation period. If an unforeseen device-related serious adverse event (SAE) or unanticipated serious adverse device effect (USADE) occurs, the end of the study will be prolonged until clinical resolution of the event.

The study or parts of the study may be discontinued by Merz North America, Inc. (Merz) or at the recommendation of an investigator after consultation with Merz at any time.

This may be based on a significant number of AEs of a similar nature that warrant such action or at the request of Merz.

Figure 2. Study design showing Radiesse® treatment visits and X-ray schedule. Group A will be subjects with MHGS grade 4 hands at enrollment. Group B will be subjects with MHGS grade 2 or grade 3 hands at enrollment.

The figure does not show the initial screening visit or follow-up visits that will be scheduled 1-month after each optional retreatment received in the study.

3. Randomization and Blinding

3.1. Randomization

The study is not a randomized trial, and there are no randomization procedures.

3.2. Blinding

The MHGS will be used to measure clinical effectiveness of the Radiesse® hand treatments by a masked evaluator performing live dorsal hand assessments. The MHGS is an ordinal scale and therefore ratings will be made based on a "snap-shot" at a time point and will not be based on a comparison to a pre-treatment photograph. The evaluator will remain masked throughout the study and blinded to knowledge of 0 to 3 repeat treatments during the study. Prior to study initiation, the masked evaluator will be trained and qualified by the study Sponsor to perform MHGS assessments. Training will consist of an instructional webinar and qualification will consist of the masked evaluator trainee scoring 225-subject photo booklets, at least 1 week apart for intra-

rater weighted Kappa analyses prior to study initiation. Retraining will occur if a minimal weighted Kappa value is not achieved (≥ 0.60), with qualification required prior to screening subjects for the study, prior to initial X-ray and Radiesse® treatment in the study. If a repeat hand treatment is scheduled during a study visit, the MHGS assessment will be completed prior to treatment. 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 (CRFs) that contain information that would break the blind.

In addition, X-rays will be taken at a licensed radiographic imaging center. Plain anteroposterior and lateral views of each hand will be taken at each required study time point. Digitized radiographic images will be transmitted to the imaging core lab to be assessed by 2 blinded, licensed radiologists.

4. Analysis Populations

There will be no formal analysis populations used. All analyses will be based on observed data available on all enrolled subjects.

5. Study Objectives

The primary objective of the study is to provide a preliminar assessment of the radiographic appearance of Radiesse® material that has been injected into the dorsum of the hands. The assessment will be with X-rays, as interpreted by a remote imaging core lab. Based on preliminary radiographic data of Radiesse® implantation in the face, it is expected that Radiesse® injection(s) in the hands will not obscure the bones as seen on plain X-rays of the hand; however, this is not being evaluated with hypothesis testing.

Other objectives of the study include evaluating the effectiveness of Radiesse® implantation for very severe volume loss in the dorsum of the hands, the rate of device/injection-related severe adverse events, the safety of multiple retreatments with Radiesse® in the dorsum of the hands. [redacted]

6. Study Endpoints and Analysis

6.1. Primary Safety Endpoints

The primary safety endpoint of the study is the incidence of obscuration of the bones of the hand at 1, 6, 12 and 24 months. The primary safety variable is number and percent of subjects with an X-ray of either hand with obscuration of the bones of the hand at 1-, 6-, 12-, and 24-months as interpreted by at least 1 of 2 blinded radiologists at the imaging core lab.

The primary event of interest is whether treatment with Radiesse® interferes with radiological assessment by obscuring the bones of the hand at any time during the study. This will be based on assessments performed post-treatment. Analysis will be made by subject, and reported. In addition, for subjects with pre-treatment assessments, paired comparisons will be made informally to assess clinically relevant issues on the pre/post treatment X-rays. Corresponding two-by-two tables for paired measurements, and 95% exact binomial confidence intervals for results by visit will be calculated. Formal hypothesis tests are not planned but nominal results from tests may be reported based on exploratory analyses and subsequently interpreted as such.

6.2. Secondary Safety Endpoints

- The rate of device/injection-related severe AEs at 1- and 6-months

AEs will be summarized descriptively using MedDRA classification version X.X including duration, severity, relationship to study device, incidence of recurrence, and need for treatment by hand. The analysis will include the incidence of all AEs at 1- and 6- months.

6.3. Other Safety Endpoints

- Incidence of all AEs over the course of the study

AEs will be summarized descriptively including type, duration, severity, relationship to study device, incidence of recurrence, and need for treatment by hand. The analysis will include the incidence of all AEs over the course of the study.

6.4. Secondary Efficacy Endpoints

The secondary efficacy variables are as follows:

- The number and percent of subjects with at least a 1 point improvement in MHGS in both hands at 1- and 6-months after initial treatment
- The number and percent of subjects with at least a 1 point improvement in MHGS in both hands at MHGS at 1- and 6-months following retreatment for those receiving retreatment
- The frequency distribution of GAIS values at 1 and 6-months after initial treatment
- The frequency distribution of GAIS values at 1- and 6-months following retreatment for those receiving retreatment
- MHQ scores at baseline, study exit, and other collected time points

Analysis will be performed to determine MHGS changes from baseline, and if treatment effects were aesthetically pleasing in the hands after treatment as reported on the GAIS. Threshold of MHGS improvement will be at least 1 point improved for effective analysis, as a percent of subjects with both hands improved. Groups A and B will be analyzed separately and in aggregate. Ninety-five percent confidence intervals will be constructed about the estimate of the proportion of subjects with improvement in both hands. Missing MHGS data will be imputed as no change.

Descriptive statistics will be provided for the MHQ at baseline, study exit, and other collected time points. The MHQ scores used for this summary will be calculated within the database or by statistical programming at the time of analysis. The MHQ scores entered by the site will not be used for this analysis.

[redacted]

- [redacted]

[redacted]

[redacted]

7. Study Subjects

7.1. Demographic, Baseline and Medical History

Demographic and baseline characteristics of enrolled subjects will be summarized. These include (but not limited to):

- Age
- Gender
- Race
- Ethnicity
- MHGS
- [redacted]

7.2. Subject Accountability

Subject disposition will be summarized as:

- Summary of subjects per visit
- Summary of early withdrawal and reason for early withdrawal.

8. Sample Size Estimation

Given that the study is a radiologic evaluation to obtain a preliminary assessment of bone obscuration, the planned sample size is not based on power calculations for a formal statistical hypothesis test, but based on a clinically relevant sample of subjects that will provide a degree of characterization regarding the ability to perform radiologic evaluations after treatment with Radiesse®. Minimizing the sample size helps prevent unnecessary exposure of subjects to radiation.

9. Poolability Analyses

Data for this post approval study are collected from a single site which invalidates the need for this type of analyses.

10. Sub-group Analyses

Sub-group analyses of the primary endpoints will be completed stratified by study group. Group A subjects will be required to present with MHGS grade 4 hands at baseline. Grade 4 hands are defined as, in the dorsal hand: very severe loss of fatty tissue and marked visibility of veins and tendons. Group B subjects will be required to present with MHGS grade 2 or 3 hands at baseline. Grade 2 and 3 hands are defined as, in the dorsal hand: moderate to severe loss of fatty tissue and mild to mode ate visibility of veins and tendons as determined by the investigator based on the MHGS.

11. Protocol Deviations

All protocol deviations encountered during the study will be listed. Each protocol deviation will be classified by the interval in which the deviation occurred and possibly by the type of deviation.