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

Development phase:	Device Post-market
Study protocol number:	P151009
Indication:	Hand augmentation to correct volume loss in the dorsum of the hand
Medical device:	Radiesse® Injectable Implant
Sponsor:	Merz North America, Inc. 6501 Six Forks Road Raleigh, NC 27615 Phone: 919.582.8000
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Primary Authors(s):	[redacted], Clinical Project Director Merz North America, Inc. [redacted], Biostatistician

[redacted]

Signature

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse event/effect
CRF	Case Report Form
DCF	Data Clarification Form
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration, US
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IFU	Instructions for use
IP	Investigational product
IRB	Institutional Review Board
MHGS	Merz Hand Grading Scale
MHGS2-3	Merz Hand Grading Scale grade 2 or 3
MHGS4	Merz Hand Grading Scale grade 4
[redacted]	[redacted]
PI	Principal investigator
PAS	Post approval study
PPS	Per protocol set
ROM	Range of Motion
SAE	Serious Adverse Event
SES	Safety evaluation set
USADE	Unanticipated serious adverse device effect
USP	United States Pharmacopeia

1 SYNOPSIS

Study title

Radiesse® Post Approval Safety Study for the Treatment of Hands With Moderate to Very Severe Dorsal Volume Loss

Study phase

Device Post-Market

Study Product

Radiesse Injectable Implant

Indication

Hand augmentation to correct volume loss in the dorsum of the hand

Study objectives

The primary objective of this study is to evaluate the safety of Radiesse implantation for very severe volume loss in the dorsum of the hands at 6 months after treatment. The primary endpoint is a non-inferiority hypothesis test to demonstrate that the proportion of subjects with device/injection-related severe adverse events (AEs) in hands that were grade 4 at baseline as determined by the Merz Hand Grading Scale[1] (MHGS, **Figure 1**) is not significantly worse than the combined proportion of subjects with device/injection-related severe AEs in hands that were MHGS grades 2 or 3 at baseline.

A secondary objective of this study is to evaluate the effectiveness of Radiesse implantation for very severe volume loss in the dorsum of the hands. The effectiveness endpoints will be measured by assessing ≥ 1 point improvement from baseline in both hands of MHGS grade 4 subjects at 3- and 6-months after initial treatment.

Another secondary objective of this study is to evaluate the safety of multiple retreatments with Radiesse in the dorsum of the hands. The hypothesis is that multiple retreatments with Radiesse do not introduce new concerns of safety.

Hand function testing will also be performed by 2 test administrators at each site to evaluate the effect of Radiesse injection on hand function. [redacted]

[1] Carruthers, et al., "A Validated Hand Grading Scale," Dermatol Surg 2008, 34:S179-S183.

Study population, diagnosis, and main criteria for in- and exclusion

A maximum of 250 subjects at least 22 years of age with moderate to very severe volume loss in the dorsum of their hands will be enrolled based on the MHGS (**Figure 1**), approximately 125 with moderate to severe volume loss (MHGS grades 2 and 3) and approximately 125 with very severe volume loss (MHGS grade 4). Exclusion criteria include participation in the pre-market Radiesse hand treatment study (Merz #P110607), previous fat injections, hand deformities, or surgery in the dorsum of the hands, and any medical condition with the potential to interfere with the study or increase the risk of AEs. See Section 7 for the full list of in- and exclusion criteria.

Study design

This is a prospective 2-year post approval study (PAS) evaluating the AE rate of MHGS baseline grade 4 hands (Group A) compared to the AE rate of MHGS baseline grade 2-3 hands (Group B). Subjects will be recruited at each site with the intention to have an equal number of subjects in Group A and Group B. All subjects will receive an initial Radiesse hand treatment in both hands, and up to 3 retreatments in the study. Hands will be assessed by evaluators on the MHGS who will be blinded to group, treatment details, time since last treatment, and number of retreatments. Subjects will assess satisfaction with treatment results on the Global Aesthetic Improvement Scale (GAIS, **Table 1**). [redacted] AE assessments will be made by the treating investigator at all study visits, and subjects will complete a 30-day take-home diary after each treatment received in the study to self-report AEs. Hand function testing will also be performed by 2 test administrators at each site to evaluate the effect of Radiesse injection on hand function. [redacted]

Duration of treatment per subject

Subjects will be in the study for approximately 24 months. Subjects will be treated with Radiesse in the dorsum of the hands at enrollment and will have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up. The retreatment interval is every 6 months as agreed upon by the treating investigator and the subject.

Total number of subjects and number of countries

There will be a maximum of 250 subjects enrolled and treated in the United States.

Number of study sites

This study will be conducted at up to 12 study sites.

2 STUDY ADMINISTRATIVE STRUCTURE

2.1 Internal responsibilities

Name	**Function**	**Address**
Merz North America, Inc.	Sponsor	Merz North America, Inc. 6501 Six Forks Road Raleigh, NC 27615

3 ETHICS

3.1 Institutional Review Board

The following documents must be submitted to the responsible Institutional Review Board (IRB): this protocol, the Informed Consent Form (ICF), relevant supporting information, and all types of subject recruitment or advertisement information. These documents must be approved by the appropriate IRB before the study is initiated. Any amendments to the protocol must also be approved, where necessary, by the IRB prior to implementing changes in the study. Documentation of these approvals must be provided to the Sponsor prior to the initiation of the amendment. The IRB used must comply with current Good Clinical Practice (GCP) and guidelines.

The investigator's responsibilities (at a minimum) regarding the IRB are as follows:

- Obtain IRB approval of the protocol, informed consent, and any advertisements to recruit subjects prior to their use.
- Obtain IRB approval for any protocol amendments and ICF revisions before implementing the changes.
- Provide the IRB with any required information before and during the study.
- Submit progress reports to the IRB, as required, during the conduct of the study; request re-review and approval of the study, as needed; provide copies of all IRB re-approvals and relevant communication to the Sponsor.
- Notify the IRB within 10 days of all serious and unexpected AEs related to the study device that are reported to the investigator by the Sponsor. The investigator is responsible for updating the IRB on the progress of the study and of any changes made to the protocol as deemed appropriate, but (in any case) at least once a year. The investigator must also keep the IRB informed of any AEs of interest, according to the IRB policy.

3.2 Ethical conduct of the study

This study will be conducted in accordance with all applicable local and federal regulations. Regulatory authorities will be notified and consulted, as required, prior to, during, and after the conduct of the study.

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH), GCP guidelines, and other applicable regulatory requirements.

3.3 Informed consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation in layman's terms regarding the nature of the study, along with the aims, methods, objectives, and any

potential risks. The ICF must be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent (if required by the IRB) prior to conducting/obtaining any study-related assessments, including the discontinuation of any medications prohibited for the study. The subject will be given a copy of the signed and dated written ICF as well as all ICF updates (if applicable).

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use of the amended form (including for ongoing subjects).

During the course of the study, the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study. In case of AEs, the subject should inform the investigator, who then will make a judgment whether continuing in the study serves the subject's best interests. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

Each ICF will contain contact information with a phone number the subject should contact if they have medical concerns 24 hours a day.

The original and any amended signed and dated ICF must be retained at the study site; and a copy must be given to the subject or subject's legally authorized representative(s).

4 INTRODUCTION

4.1 Study background

The clinical study is a 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, to provide safety and effectiveness data in subjects with more severe volume loss (MHGS grade 4) than those subjects evaluated in the pre-market study. The pre-market (Merz protocol #P110607) study cohort excluded subjects with baseline grade 4 hands. This study will also provide additional data specific to safety of multiple retreatments.

4.2 Study rationale

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 MHGS (**Figure 1**), these were hands rated as grade 2 or grade 3 at baseline, or before treatment. On the MHGS, these hands had moderate to severe dorsal volume loss. Subjects with MHGS grade 4 (MHGS4) hands at baseline, or very severe dorsal volume loss, were excluded from the pre-market study. With the Food and Drug Administration (FDA) approval of Radiesse for treatment of the hands, it is anticipated that patients that present with MHGS4 hands will seek treatment. This PAS will evaluate the safety and effectiveness of Radiesse treatment in MHGS4 hands with very severe dorsal volume loss. 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.

A non-inferiority hypothesis test will be conducted for the primary study endpoint. The hypothesis test will compare the 6-month rate of device/injection-related severe AEs in the MHGS4 subjects (Group A) versus a subjects with baseline MHGS grade 2 or grade 3 (MHGS2-3, Group B).

4.3 Risk-benefit assessment

Potential risks associated with the injection of Radiesse into the dorsum of the hand to restore volume loss are similar to injections performed with any other commercially available cosmetic dermal filler, such as bruising, swelling and redness. For complete safety and risk information, see the Instructions For Use (IFU, **Appendix A**). Lidocaine is approved as a local and regional anesthetic and will be mixed in-office with Radiesse. Potential side effects associated with lidocaine are a risk of participating in this study and include lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, ringing noise in the ears, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest, slow heartbeat, hypotension, and cardiovascular collapse, which may lead to cardiac arrest. However, these side effects are unlikely to occur at the low

doses of lidocaine being used in this investigation. Lidocaine is beneficial in terms of pain reduction during and after the study procedure.

A potential benefit of participating in this study is to have correction of volume loss and reduction of the prominence of veins and tendons in the dorsum of one or both hands. Additional potential benefits of improving the appearance of the hands could include enhanced emotional well-being with improved satisfaction with the appearance of the hands, or the perception of having a more youthful appearance.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The primary objective of this study is to evaluate the safety of Radiesse implantation for very severe volume loss in the dorsum of the hands.

Secondary objectives of this study include evaluation of the effectiveness of Radiesse implantation for very severe volume loss in the dorsum of the hands, the safety of multiple retreatments with Radiesse in the dorsum of the hands, and to support the hypothesis that multiple retreatments with Radiesse do not introduce new concerns of safety.

Hand function testing will also be performed by test administrators at each site to evaluate the effect of Radiesse injection on hand function. [redacted]

5.2 Endpoints

The primary safety endpoint of the study is the 6-month rate of device/injection-related severe adverse events

The secondary endpoints of the study are:

- The rate of device/injection-related severe adverse events at 24 months
- 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
- Hand function testing at baseline, study exit, and other collected time points
    - Inter-rater correlation of hand function testing results for each site
        - Differences between sites in hand function testing results

[redacted]

Figure 1. Merz Hand Grading Scale (MHGS).

Table 1. Global Aesthetic Improvement Scale (GAIS).

6 INVESTIGATIONAL PLAN

6.1 Overall 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 MHGS4 subjects. The primary objective of evaluating the safety of treatment of MHGS4 subjects will be comparing the 6-month rate of device/injection-related severe AEs in the MHGS4 group (Group A) versus the MHGS2-3 group (Group B). 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 up to 12 investigational sites in the United States.

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

- Hand function testing - to be performed by two site hand function testers for first 10 subjects enrolled at each site, and by one hand function tester for all other subjects enrolled at each site - to evaluate measurable functional effect(s) of Radiesse injection on hand function. A minimum of 50 subjects across all sites will be evaluated by two independent hand function testers.

- MHGS (**Figure 1**)– a single blinded site evaluator will grade the hands using the MHGS

- Photographs – at baseline and exit from the study, and during the study to document a serious or medically concerning adverse event in the hands. At the 2-week follow-up visit, hand photographs will also be taken in subjects who have a device and/or injection-related severe adverse event.

- [redacted]

- GAIS (**Table 1**) – subjects will rate the aesthetically pleasing aspect of the Radiesse hand treatment using the GAIS

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

6.1.1 Study visits

Subjects will be required to present for 8 to 11 in-office visits and receive 1 to 4 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 8 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) and a visit scheduled 1-month after each repeat treatment.

The Visits will include a Screening/Enrollment/Baseline Visit in which the subject receives their first injections of Radiesse. After Enrollment, there will be a 72-hour follow-up phone call made to each subject to assess AEs and/or any changes in concomitant medications. Subjects will be seen at the study site for follow up visits at Months 1, 3, 6, 12, 18, and 24. If they are administered repeat injections at any of the Months 6, 12 and 18 visits, they will receive a 72-hour follow-up phone call following each injection and return for follow up visits 1 month post-injection at Months 7, 13, and/or 19 respectively.

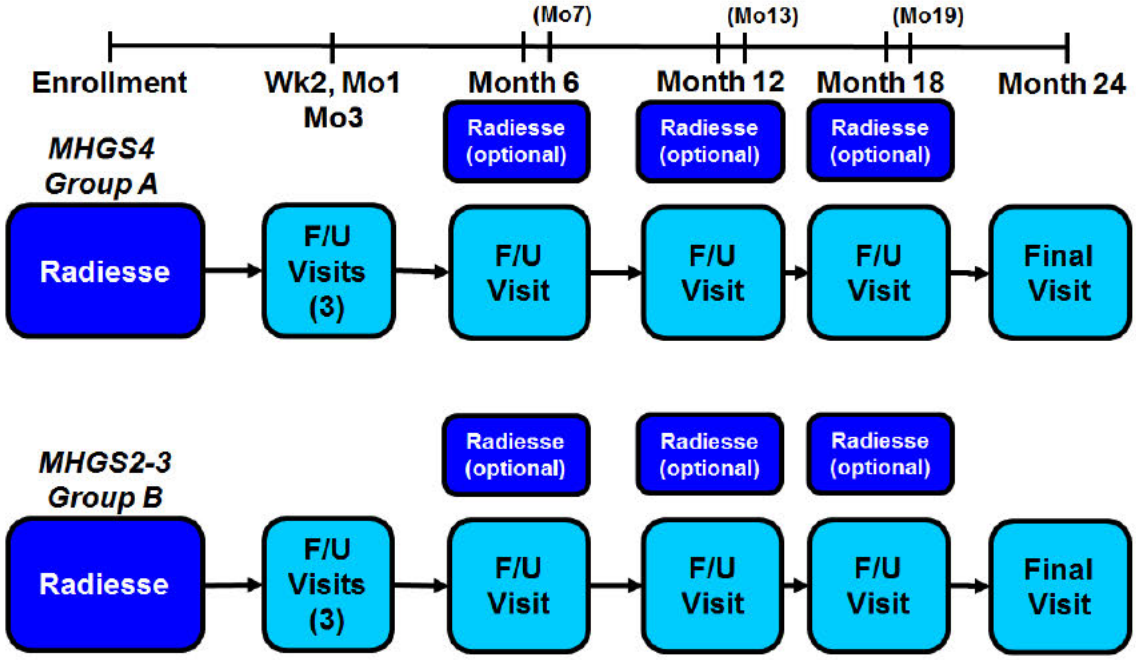
6.1.2 End of study

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 device effect (USADE) occurs, the end of the study will be prolonged until clinical resolution of the event, or considered permanent as determined by the treating investigator.

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.

6.1.3 Study flow chart

Figure 2. Study design showing Radiesse treatment and follow-up visit schedule. In parentheses over the timeline are the follow-up visits that will be scheduled only if a repeat treatment is received at the 6-, 12-, or 18-month visit.



6.1.4 Study timeline

Milestone	Relative to date of FDA Approval
Expected date of study initiation (First subject enrolled)	4 months
Expected monthly number of study sites with IRB approvals	4
Expected number of subjects enrolled per month	90
Expected date for completion of subject enrollment (Last subject, first visit)	7 months
Six Month Post-Approval Report to FDA	6 months
One Year Post-Approval Report to FDA	12 months
Eighteen Month Post-Approval Report to FDA	18 months
Two Year Post-Approval Report to FDA	24 months
Expected date for completion of study follow-up (Last subject last visit)	31 months
Expected date for submission of final report	34 months

7 STUDY POPULATION

The study will enroll adults at least 22 years of age. There will be 2 study groups, with approximately 125 subjects enrolled into each 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 moderate visibility of veins and tendons. Group A subjects will provide safety and effectiveness of Radiesse treatment of MHGS grade 4 hands, which might receive higher injection volumes than hands of Group B subjects. Every effort will be made to have all enrolled subjects complete the study. If subjects are withdrawn or lost to follow during the study, they will not be replaced.

7.1 Selection of study population

Presenting subjects will be screened to the selection criteria identified in sections 7.2 and 7.3 below. The investigational site will recruit candidates and perform the screening, which could include use of patient databases, phone calls, email or postal mail distribution, and advertisements.

7.2 Inclusion criteria

Only subjects meeting all of the following inclusion criteria will be considered for study enrollment:

1. Has hands rating 2, 3, or 4 on the validated MHGS as determined by a live, masked evaluator.
    - Left and right hand with a rating of 4 of the validated MHGS will be assigned to Group A.
    - Left and right hands with a rating of 2 or 3 on the validated MHGS will be assigned to Group B.
2. Has left and right hands with a rating of 2 or 3 on the validated MHGS as determined by a live, masked evaluator if screened for Group B.
3. Is at least 22 years of age.[2]
4. Has signed an ICF.

[2] Pediatric populations or subpopulations generally do not suffer from the hand condition the device is intended to treat in the study protocol.

5. Understands and accepts the obligation not to receive any other procedures in the dorsum of the hands through the end of the study.

6. Understands and accepts the obligation and is logistically able to present for all scheduled follow-up visits and meet all study requirements.

7.3 Exclusion criteria

Subjects having any of the following criteria, either at screening or at baseline, will not be included in the study:

1. Was a participant in the Radiesse hands pre-market clinical study (Merz #P110607).

2. Has been treated with fat injections or Radiesse in the hands, has hand deformities, or has received surgery in the dorsum of the hands.

3. Has received within the past 6 months or plans to receive during the study dermal resurfacing procedures (e.g. chemical peel, dermabrasion, ablative laser resurfacing) or non-invasive skin-tightening (e.g. Thermage, Ulthera) in the dorsum of the hands during the study.

4. Has received in the past 2 weeks or plans to receive during the study, prescription wrinkle therapies, topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) in the dorsum of the hands during the study.

5. Has received in the past 2 months, or plans to receive immunosuppressive medications or systemic steroids (intranasal / inhaled steroids acceptable) during the study.

6. Has an acute inflammatory process or infection, or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of AEs.

7. Has a known bleeding disorder or is receiving medication that will likely increase the risk of bleeding as the result of injection.

8. Has a known history of allergic / anaphylactic reactions, including hypersensitivity to lidocaine or anesthetics of the amide type, or any of the device components.

9. Has a known history of hyper- or hypo-pigmentation, keloid formation, or hypertrophic scarring.

10. Is a female of child bearing potential[3] and not using medically effective[4] birth control or is pregnant or lactating.

[3] Childbearing potential is defined as NOT premenarche, permanently sterilized or postmenopausal (i.e., 12 months with no menses without an alternative medical cause).

11. Has any other medical condition with the potential to interfere with the study or increase the risk of AEs, such as: autoimmune disease affecting the hand, hand implants, Dupuytren's contracture, history of hand tumor, vascular malformations, Raynaud's disease, and patients at risk for tendon rupture.

12. Is enrolled or plans to enroll in an interfering study.

13. Is an employee or direct relative of an employee of the investigational site or of the study Sponsor.

7.4 Removal of subjects from treatment or assessment

7.4.1 Discontinuation of subjects

The subject may discontinue from the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled. Date and discontinuation circumstances should be recorded.

Subjects must be discontinued from the study by the investigator at any time for any of the following reasons:

- Withdrawal of informed consent.
- Pregnancy.
- Any AE for which treatment continuation would constitute an unacceptably high risk for the subject.

Before discontinuation, every effort should be made to ensure that the subject returns for a final study visit. In the case of loss to follow-up subjects, every effort should be made to contact subjects lost to follow-up, and all such efforts should be documented in the subject file.

7.4.2 Premature termination or suspension of the study or a study site

The study or the study site can be prematurely terminated or suspended by the sponsor. If and when certain issues arise affecting the conduct of this Post Approval Study, the possibility of early study termination will be discussed with the FDA prior to termination. Reasons for termination of the study or a study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory.

[4] Defined as a method that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or vasectomized partner.

- The risks and benefits of continuing the study have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data do not justify a continuation of the study.
- The investigator or study site exhibit serious and/or persistent non-adherence to the clinical study protocol and/or applicable regulatory requirements.
- The Sponsor decides to terminate the study at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the IRB makes a recommendation to terminate or suspend approval for the study, the study site, or the investigator.

If the study is prematurely terminated or suspended for any reason, the investigator must inform the subjects and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the Sponsor will promptly inform the investigators, study sites, the IRB, and regulatory authorities of the termination or suspension of the study, as appropriate.

8 TREATMENTS

8.1 Investigational product(s)

8.1.1 Description of investigational product(s)

Radiesse injectable implant is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant. The principle component is synthetic calcium hydroxylapatite suspended in a gel carrier that consists primarily of water (sterile water for injection USP), glycerin (USP), sodium carboxymethylcellulose (USP). Radiesse injectable implant (1.5cc syringe unit) has a CaHA particle size range of 25-45 microns and should be injected with a 25 gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle. The same size needle should be utilized throughout the trial for an individual subject and needle size will be collected in the electronic case report form.

8.1.2 Disposition of investigational product(s)

Radiesse has been FDA approved for injection into the face since 2006 (PMA P050037 and PMA P005052), and was approved for hand augmentation to correct volume loss in the dorsum of the hand in 2015 (PMA P050052/S049, see IFU **Appendix A**). This same Radiesse formulation will be used in the study for injection, as approved in the indication for hand augmentation to correct volume loss in the dorsum of the hand. Radiesse will be mixed with 2% lidocaine HCl prior to injection – an approved use of Radiesse.

8.2 Treatment administration

8.2.1 Randomization Procedures

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

8.2.2 Treatment method

Prior to injection, Radiesse will be mixed with 0.26cc of 2% Lidocaine HCl. Volume injected as well as any observed AEs will be recorded. A maximum of 2 1.5cc Radiesse syringes will be injected per hand, per treatment visit. Treatment and retreatment visits will be scheduled per Table 2. There will be no touch-up treatments performed in the study. Subjects are to be given a 30-day take-home diary on which to record AEs that may occur before their next visit (copy provided in **Appendix B**).

Step-by-step injection instructions are as indicated below from the IFU in **Appendix A**.

Technique for Mixing Radiesse injectable implant and 2% Lidocaine HCl

The following components are required for the percutaneous injection procedure and mixing Radiesse injectable implant with lidocaine:

- Radiesse injectable implant syringe(s) – 1.5cc
- Sterile 27 gauge, 0.5" regular-wall needle with luer lock connector
- 3.0cc sterile polypropylene luerlock syringe ([redacted]
- 0.2cc of 2% lidocaine HCl for injection, USP solution (not supplied by Merz North America, Inc.)
- Sterile Female-to-female luer lock connector [redacted]

The Radiesse, sterile needles, 3.0cc sterile polypropylene mixing syringe [redacted]), and the female-to-female luer lock connector [redacted]) will be provided in a kit by Merz for the study. The lidocaine will not be supplied by Merz.

Component Assembly and Mixing Instructions

1. Remove foil pouch from the carton containing the Radiesse injectable implant syringe. Open the foil pouch by tearing at the notches (marked 1 and 2), and remove the syringe from the foil pouch. *There is a small amount of moisture normally present inside the foil pouch for sterilization purposes; this is not an indication of a defective product.*
2. Assemble the components and perform the mixing using sterile technique (see **Figure 3**).

Figure 3. Radiesse mixing components. Left to right: Female-to-female luer lock connector, Radiesse 1.5cc syringe, 3.0cc mixing syringe, sterile 27 gauge, 0.5" needle

[redacted]

3. Draw the 0.2cc lidocaine into a 3.0cc sterile polypropylene mixing syringe fitted with a sterile 27 gauge, 0.5" needle.
4. Tap the mixing syringe, containing 0.26cc lidocaine and depress its push rod to remove all excess air.

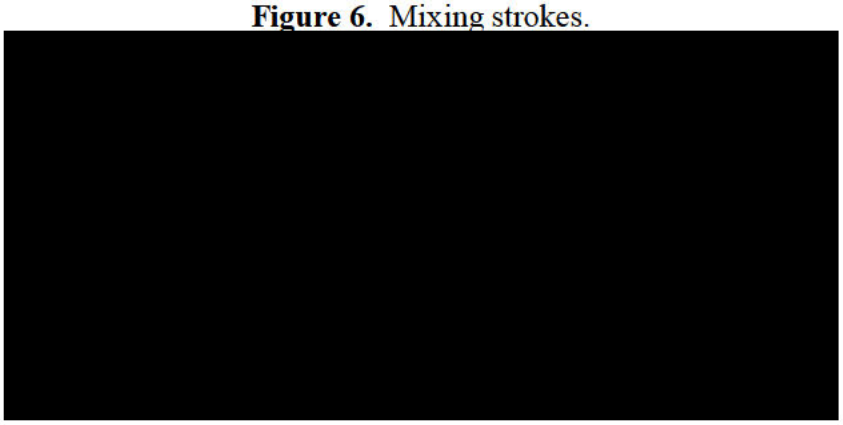
5. Remove the sterile 27 gauge, 0.5" needle.
6. Remove the luer syringe cap from the distal end of the Radiesse syringe and firmly connect the mixing syringe to the Radiesse syringe using the female-to-female luer lock connector (see **Figures 4** and **5**).

Figure 4. Removal of cap from Radiesse syringe.

Figure 5. Connecting Radiesse syringe to the mixing syringe.

7. Mix the lidocaine and Radiesse by alternately depressing the plungers, first on the mixing syringe and then on the Radiesse syringe for 10 mixing strokes (each mixing stroke is 1 complete compression of the mixing syringe plunger followed by 1 complete compression of the Radiesse syringe plunger). Plungers are compressed firmly and quickly, at about 2 compressions per second (**Figure 6**).

Figure 6. Mixing strokes.



8. After mixing, remove the mixing syringe and the female-to-female luer lock connector and discard.
9. Fit the syringe containing the lidocaine and Radiesse mixture with a 27 ID gauge injection needle by twisting the syringe of Radiesse onto the luer lock fitting of the needle. *Tighten the needle securely to the syringe.* If excess Radiesse is on the surface of the luer lock fittings, it will need to be wiped clean with sterile gauze.
10. Proceed to the "Injection Procedure" below.

Injection Procedure for Hand Augmentation

1. Prepare subject for percutaneous injection using standard methods. Have the subject wash both hands with soapy water producing friction for 5-10 minutes and then prepare hands with suitable antiseptic. The treatment injection site may be marked for planned injection sites. Jewelry should be removed prior to injection and until post-procedure swelling has resolved.

2. Using the syringe of Radiesse injectable implant that has been mixed with lidocaine using the procedure described in "Mixing Instructions" above, and fitted with the injection needle, slowly push the syringe plunger until Radiesse injectable implant extrudes from the end of the needle performing aspiration before bolus injection to avoid intravascular injection. If leakage is noted at the luer fitting, wipe it clean with sterile gauze. It may be necessary to tighten the needle, remove the needle and clean the surfaces of the luer fitting or, in extreme cases, replace both the syringe and the needle. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe.

3. Locate the initial site for injection. Subjects are to receive injections in the dorsum of the hands between the 1st and 5th metacarpals. Injection should initially occur between the 2nd and 4th metacarpals, taking care not to inject close to the metacarpophalangeal joints. If necessary to achieve optimal correction, injection is also allowed between the 1st and 2nd, and 4th and 5th metacarpals.

4. Skin tenting should be performed to separate the skin from vascular and tendinous structures by using the thumb and forefinger of the non-injecting hand to lift skin over the dorsal aspect of the hand being treated.

5. Advance the needle between the subcutaneous layer and superficial fascia with the syringe parallel to the dorsum of the hand. Carefully push the plunger of the Radiesse injectable implant syringe to start the injection and inject the Radiesse injectable implant material in small boluses, 0.2 – 0.5cc/bolus. No more than 0.5cc should be injected per bolus. The number of boluses will vary depending on the extent of treatment desired. No more than 3cc of Radiesse injectable implant (2 syringes) will be injected per hand, per treatment session.

6. If significant resistance is encountered when pushing the plunger, the injection needle may be moved slightly to allow easier placement of the material or it may be necessary to change the injection needle.

7. Immediately after injection, cover the injection site with a sterile 4x4 gauze and have the subject sit on this hand while the contralateral hand is being injected. This warms the Radiesse injectable implant making it more malleable for later massaging.

8. Treat the contralateral hand in the same manner as described in steps 2 through 6 above.

9. Immediately after injection of the contralateral hand, cover the injection site with a sterile 4x4 gauze and have the subject sit on this hand.

10. While the contralateral hand is warming, remove the gauze from the hand that was initially injected, have the subject make a fist with this hand, and gently massage the dorsum of the hand until Radiesse has been evenly spread across the dorsum, remaining distal to the wrist crease and proximal to the metacarpophalangeal joints.

11. Use a 1:1 correction factor. No overcorrection is needed.

9 STUDY ASSESSMENTS

9.1 Clinical evaluations

9.1.1 Training and masking of MHGS evaluators

The MHGS (**Figure 1**) will be used to measure clinical effectiveness of the Radiesse hand treatments by a masked evaluator performing live dorsal hand assessments. There will be one masked MHGS evaluator per site. 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 2 25-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 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.

9.1.2 Evaluation of aesthetic improvement

To assess the aesthetically pleasing aspect of the Radiesse hand treatment outcomes, subjects will perform self-assessments on the GAIS shown in **Table 1**. The GAIS is a relative scale therefore the subjects will be asked to perform the rating compared to baseline pre-treatment photographs.

9.1.3 Evaluation of hand function

Hand function data will be collected at enrollment and at 5 to 8 follow-up visits in all subjects with the tests listed below. [redacted]

Hand function testing performed in the study will include:

- **Range of Motion** (ROM). The rROM will be assessed using a Jamar finger goniometer (Sammons Preston Rolyan, Bolingbrook, IL). This test will passively and actively measure the angle of motion of all 5 metacarpophalangeal joints in each hand by determining the flexion and extension angles. The flexion will determine how far each finger can be flexed at the metacarpophalangeal joint towards the palm. The extension will determine how each finger can be extended at the metacarpophalangeal joint away from the palm.

- **Sensation**. Sensation in the dorsum of each hand will be Semmes-Weinstein monofilament touch test whereby the subject will be asked to report when a light touch is felt at different areas of the dorsum of each hand.

- **Dexterity**. Fine motor skills (dexterity) will be assessed using the Functional Dexterity Test (FDT) which assesses one's ability to use the hand for daily tasks requiring 3-jaw chuck prehensions, i.e. buttoning, tying shoelaces, screwing a nut and bolt and lacing yarn. Dexterity will be measured using a 16-hole peg board (North Coast Medical, Inc., Morgan Hill, CA).

- **Strength**. Hand strength will be assessed in 2 ways; grip and pinch strengths. The grip strength will be assessed using a standard, adjustable-handle Jamar hydraulic hand dynamometer (Sammons Preston Rolyan, Bolingbrook, IL). The pinch strength will be assessed in three different ways; tip (two-point) pinch, key (lateral) pinch and palmar (three-jaw chuck) pinch using the Jamar hydraulic pinch gauge (Sammons Preston Rolyan, Bolingbrook, IL).

For the first 10 subjects enrolled at each site, hand function testing will be performed by 2 independent evaluators. After the first 10 subjects, only one evaluator will be performing the hand function testing at the required timepoints. This data will provide an assessment of intra and inter-rater variability in hand function measures within and between sites. A minimum of 50 subjects across all sites will be evaluated by two independent hand function testers.

Training of the investigators who will be conducting the hand function tests on subjects will be provided by an instructional video of a hand surgeon and hand therapist. Sponsor trainers will be qualified by direct interaction with the hand surgeon who created and co-demonstrates the testing in the instructional video. Sponsor trainers worked closely with the hand surgeon during the creation of instructional video and creation of the hand function test protocol (Appendix E). To qualify, investigator trainees will be required to complete the instructional video and demonstrate to the Sponsor trainer the required competencies in accordance with the protocol for hand function testing during the Sponsor-monitored on-site training. Selection of trainees will include targeting investigators who plan to remain on staff for at least two years. Training certificates will be issued upon completion of trainee qualification. Only staff members who have been trained and qualified will be allowed to perform hand function testing during the study.

Hand function test investigators will not be blinded in the study to subject group, time(s) of treatment, and time since last treatment.

9.2 Visit schedule

Screening and Enrollment

Enrollment will be limited to 250 subjects for the study. The Sponsor will oversee enrollment and be in direct communication with the investigational sites to make all efforts not to exceed the enrollment target of 250 subjects, and to ensure that Groups A and B (described in Section 7) are fully enrolled. Presenting subjects may be pre-screened to the selection criteria identified in Sections 7.2 and 7.3 above. If it is determined that a presenting subject meets these selection criteria, the subject will be given an ICF to review and sign.

Upon the subject's provision of informed consent to participate in the study, the subject will be enrolled in the study and assigned a study ID number. The number will contain 3 parts – trial identification code (GF = GradeFour), site identification number, and subject enrollment order number. For example, the third subject enrolled will receive study ID number GF-1-03. The masked evaluator will assess hands on the MHGS to meet hand rating requirements for inclusion. Enrolled subjects will be assigned to Group A or B based on baseline MHGS ratings until both groups are fully enrolled. Females of childbearing age will complete a urine pregnancy test. Study information including demographics and concomitant medications will be recorded, and photographs will be taken of each hand. After photographs, subjects will complete [redacted] all of the hand function tests. If the subject is one of the first 10 enrolled at a site, the hand function tests will be repeated, as administered by a different hand function testing investigator. At this time, subjects will receive a Radiesse treatment. A take-home 30-day diary will be given to the subject. A physician will assess the subject's hands for AEs. Subjects will be scheduled for a phone visit to be conducted 72 hours after treatment.

Follow-Up Evaluations

72 hours after enrollment: All subjects will be scheduled for a phone visit 72 hours after initial treatment to assess for AEs. Subjects will be reminded to continue daily entries into their 30-day diary.

Week 2: 14 ± 3 days from enrollment, all subjects will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. Subject self-assessment of aesthetic improvement will be performed using the GAIS. [redacted] Completed entries in the take-home 30-day diary will be reviewed for completion and collected. A physician will assess the subject's hands for AEs. Photographs of the hands will be taken in the event of a device and/or injection-related severe AE, or a serious or medically concerning AE.

Month 1: 30 ± 5 days from enrollment, all subjects will return for a follow-up visit. [redacted] Changes in concomitant medications will be recorded by the study staff. [redacted] Completed entries in the take-home 30-day diary will be reviewed for completion and collected. A physician will assess the subject's hands for AEs. Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 3: 90 ± 7 days from enrollment, all subjects will return for a follow-up visit. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Changes in concomitant medications will be recorded by the study staff. Subject self-assessment of aesthetic improvement will be performed using the GAIS. [redacted] A physician will assess the subject's hands for AEs. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 6: 180 ± 10 days from enrollment, all subjects will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. [redacted] A physician will assess the subject's hands for AEs. [redacted] Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Retreatment may be performed at this visit after all study data have been collected at this visit [redacted] if both the treating investigator and the subject agree. Females of childbearing age will complete a urine pregnancy test before retreatment if a retreatment is to be performed during this visit. If performed, the subject will receive another 30-day take-home diary on which to record AEs.

72 hours after Month 6 retreatment: Only subjects receiving a retreatment at the Month 6 visit will be scheduled for a phone visit 72 hours after treatment to assess for AEs. Subjects will be reminded to continue daily entries into their 30-day diary.

Month 7: 210 ± 5 days from enrollment, only subjects receiving a retreatment at Month 6 will return for a follow-up visit. [redacted] The take-home 30-day diary will be reviewed for completion and collected. A physician will assess the subject's hands for AEs. [redacted] Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 12: 360 ± 30 days from enrollment, all subjects will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. [redacted] A physician will assess the subject's hands for AEs. Completed entries in the take-home 30-day diary will be reviewed for completion and collected. [redacted] Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Retreatment may be performed at this visit after all study data have been collected at this visit [redacted] if both the treating investigator and the subject agree. Females of childbearing age will complete a urine pregnancy test before retreatment if a retreatment is to be performed during this visit. If performed, the subject will receive another 30-day take-home diary on which to record AEs.

72 hours after Month 12 retreatment: Only subjects receiving a retreatment at the Month 12 visit will be scheduled for a phone visit 72 hours after treatment to assess for AEs. Subjects will be reminded to continue daily entries into their 30-day diary.

Month 13: 390 ± 5 days from enrollment, only subjects receiving a retreatment at Month 12 will return for a follow-up visit. [redacted] The take-home 30-day diary will be reviewed for completion and collected. A physician will assess the subject's hands for AEs. [redacted] Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 18: 540 ± 15 days from enrollment, all subjects will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. [redacted] A physician will assess the subject's hands for AEs. Completed entries in the take-home 30-day diary will be reviewed for completion and collected. [redacted] Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Retreatment may be performed at this visit after all study data have been collected at this visit [redacted] if both the treating investigator and the subject agree. Females of childbearing age will complete a urine pregnancy test before retreatment if a retreatment is to be performed during this visit. If performed, the subject will receive another 30-day take-home diary on which to record AEs.

72 hours after Month 18 retreatment: Only subjects receiving a retreatment at the Month 18 visit will be scheduled for a phone visit 72 hours after treatment to assess for AEs. Subjects will be reminded to continue daily entries into their 30-day diary.

Month 19: 570 ± 5 days from enrollment, only subjects receiving a retreatment at Month 18 will return for a follow-up visit. [redacted] The take-home 30-day diary will be reviewed for completion and collected. A physician will assess the subject's hands for AEs. [redacted] Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 24: 720 ± 30 days from enrollment, all subjects will return for the final follow-up visit. Changes in concomitant medications will be recorded by the study staff. [redacted] A physician will assess the subject's hands for AEs. Hand function testing will be performed twice if the subject is one of the first 10 enrolled at a site (e.g., GF-x-01 through GF-x-10), and once if enrolled as the 11th or after (e.g., GF-x-11 and beyond). Photographs of the hands will be taken. Females of childbearing age will complete a urine pregnancy test. The subject's study participation will end at this visit.

Unscheduled Visits: Subjects will be instructed to call the investigational site if they experience significant hand discomfort or difficulty performing activities at any point during the 24 month period. At the discretion of the treating investigator, a subject will be requested to appear for an unscheduled study visit for follow-up and potential intervention for an AE of concern. For an unscheduled visit, the subject will be assessed for AEs, concomitant medication update will be obtained, [redacted] and photographs of the hands will be taken.

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 device effect (USADE) occurs, the end of the study will be prolonged until clinical resolution of the event, or considered permanent as determined by the treating investigator.

Table 2. Schedule of Events.

Assessment	Screening/ Enrollment	Wk 2	Mo 1	Mo 3	Mo 6	Mo 7†	Mo 12	Mo 13†	Mo 18	Mo 19†	Mo 24
Visit Window (Day)	-14 to 0	Day 14 +-3	Day 30 +- 5	Day 90 +-7	Day 180 +- 10	Day 210 +-5	Day 360 +- 30	Day 390 +-5	Day 540 +- 15	Day 570 +-5	Day 720 +- 30
Inclusion/ Exclusion	X										
Informed Consent	X										
Demographics	X										
Concomitant Medications	X	X	X	X	X		X		X		X
Merz Hand Grading Scale – Masked Evaluator	X		[redacted]	X	[redacted]						
Hand Function Testing	X††		X††		X††	X††	X††	X††	X††	X††	X††
[redacted]											
Subject GAIS		X	[redacted]	X	[redacted]						
Urine Pregnancy Test	X				X‡‡		X‡‡		X‡‡		X
Hand Treatment	X				X*		X*		X*		
72-hour follow-up phone call	X				X**		X**		X**		
Adverse Events – Subject Diary	X	X	X		X**	X	X**	X	X**	X	
Adverse Events – Treating MD	X	X	X	X	X	X	X	X	X	X	X
Hand Photographs	X	X∞	X‡	X‡	X‡	X‡	X‡	X‡	X‡	X‡	X

† No visit if no treatment received one month prior
* Treatment decision at the discretion of the Treating MD in agreement with subject
†† To be performed by 2 hand function testers for first 10 subjects enrolled at each site, and by one hand function tester for all other subjects enrolled at each site.
‡ Only to document a serious or medically concerning adverse event
‡‡ Only if retreatment is to be received at this visit
** Only if retreatment is received at this visit
∞ Only to document a device and/or injection-related severe AE, or a serious or medically concerning AE

10 SAFETY ASSESSMENTS

All AEs observed by study subjects, investigators or other study staff from informed consent through last study follow up visit will be recorded. If a SAE or unanticipated serious device related effect (USADE) occurs, study subjects may be requested to appear for unscheduled follow up visits for AE assessment and hand photographs.

The following information, at minimum, must be recorded:

- AE description
- AE type (serious, expected, unexpected) – Refer to definitions below
- Start and Stop Dates
- Intensity (mild, moderate, severe) – Refer to definitions below
- Causal relationship (not related, related) – Refer to definitions below
- Treatment description, if any

10.1 Definition of intensity

The clinical intensity of an AE will be classified as:

Mild: Signs and symptoms that can be easily tolerated. Symptoms can be ignored and disappear when the subject is distracted.

Moderate: Signs and symptoms that cause discomfort and interfere with normal functioning, but are tolerable. They cannot be ignored and do not disappear when the subject is distracted.

Severe: Signs and symptoms that affect usual daily activity and incapacitate the subject, thereby interrupting his/her daily activities.

The definitions above are difficult to apply for some data (e.g., clinically relevant laboratory values that are documented and evaluated on the CRF AE report form). In such situations, the investigator should make a judgment based on personal experience.

10.2 Definition of causal relationship

An AE is considered to be "related" to investigational product (IP) if a causal relationship between the IP and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out) in the opinion of the investigator.

The expression "reasonable causal relationship" is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship (ICH E2A guideline). Otherwise, the relationship should be considered as "not related."

10.3 Definition of type

10.3.1 Adverse event

The general definition for an AE is an untoward medical occurrence which does not necessarily have a causal relationship to the investigational product.

10.3.2 Serious adverse event

A SAE is an AE that meets at least 1 of the following 6 criteria:

(1) Results in death.

(2) Is life-threatening.[5]

(3) Requires inpatient hospitalization, or prolongation of existing hospitalization.

(4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

(5) Is a congenital anomaly/birth defect.

(6) Is an important medical event[6], including an event that requires medical or surgical intervention necessary to preclude permanent impairment of a body function or permanent damage to a body structure.

All SAEs that occur during the study period, whether considered to be related to the IP or not must be reported by e-fax (1-336-458-5983) or e-mail sent within 24 hours of knowledge of the event.

Please send completed SAE forms to: adverse.events@merz.com
Product Safety Department
Merz North America, Inc.
6501 Six Forks Road
Raleigh, North Carolina 27615

[5] Defined as the subject being at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

[6] According to ICH E2A, CPMP/ICH/377/95: "Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse."

Although all information required for completion of an SAE report form may not be available within the specified time period, the following minimal initial information should be reported: Subject ID #, Site #, name and contact information (of investigator/study coordinator), and which of the 6 SAE criteria identified above resulted in the event being deemed "serious".

IRB reporting requirements may also apply for SAEs.

10.3.3 Unanticipated adverse device effect

An unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the IFU or Radiesse labeling, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.3.4 Expected adverse events

An expected AE is an experience listed in the current IFU (**Appendix A**).

10.3.5 Unexpected adverse events

An unexpected AE is an experience not previously reported in nature, severity, or incidence in the current IFU. IRB reporting requirements may also apply.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

This study will be monitored in accordance with GCP and regulatory guidelines. By signing this protocol, the investigator agrees to periodic, on-site monitoring of all appropriate study documentation. The progress of the study will be monitored by periodic on-site visits and frequent communications between the Sponsor (or designee) and the investigator (either by phone, fax, email, or post). During these contacts, the monitor will:

- Check and assess the progress of the study.
- Conduct source document verification to ensure data are authentic, accurate, and complete.
- Identify any issues and address their resolution.
- Ensure the safety and rights of subjects are being protected.
- Verify that the study is being conducted in accordance with the currently approved protocol (and any amendments) per GCP and all applicable regulatory requirements.

In addition, the monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits.

11.2 Audits / Inspections

Audits may be performed, including the possibility that a member of the sponsor's quality assurance function or their representative may arrange to visit the investigator in order to audit the performance of the study at the study site, as well as all study documents originating there.

Inspections by regulatory authority representatives and IRBs are possible at any time, even after the end of study. The investigator is to notify the Sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IRB and/or regulatory authorities, and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

12 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of study planning.

Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close will be summarized in the clinical study report.

12.1 Determination of sample size

The primary endpoint will be based on a non-inferiority hypothesis test comparing the 6-month rate of device/injection-related severe AEs in the MHGS4 (Group A) subjects versus the MHGS2-3 (Group B) subjects. 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 MHGS4 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. Safety and effectiveness data that are collected after 6 months and up to 2 years will be presented descriptively.

12.2 Analysis sets

The safety and per protocol analysis sets will be used for analysis of the study. Differences in results between analysis sets will be explored.

12.2.1 Safety Evaluation Set (SES)

The SES is the subset of all subjects who were exposed to the study device at enrollment. This will be the basis of the primary analysis of the primary safety endpoint.

12.2.2 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.

12.3 Variables for analysis

12.3.1 Primary safety variable

The primary safety variable is evaluation of 6-month rate of device/injection-related severe AEs in MHGS4 (Group A) subjects versus MHGS2-3 (Group B) subjects.

12.3.2 Primary efficacy variable

The primary efficacy variable is the 3-Month MHGS value relative to baseline, with improvement defined by at least 1 point on the MHGS in both hands.

12.3.3 Secondary [redacted] and safety variables

The secondary [redacted] and safety variables in the study are:

[redacted]

- GAIS results at [redacted] 3-, [redacted] after initial treatment, and 1-month after each retreatment.
- The rate of device/injection-related severe AEs at 24 months.

[redacted]

- Numbers and percentage of subjects experiencing AEs up to 24-months after enrollment, after receiving 1 to 4 treatments in the study.
- Hand function test results up to 24-months after enrollment.
- Correlation of 2 hand function test investigators at each site, and functional data between sites.

12.4 Statistical analysis methods

12.4.1 Primary safety variable

The primary endpoint analysis will be based on a non-inferiority hypothesis test. Stated as a null and alternative hypothesis test:

Ho: $P_A - P_B \geq 12\%$

Ha: $P_A - P_B < 12\%$

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. The test will be based on the Farrington-Manning likelihood score test and a one-sided 0.05 alpha level.

12.4.2 Secondary [redacted] and safety variables

The numbers and percentages of subjects experiencing events will be reported by visit. Descriptive statistics will be provided for all study endpoints. Corresponding 95% confidence intervals will be calculated as appropriate.

Events of interest include AEs, as well as efficacy outcomes, including GAIS results (i.e. any improvement vs. no improvement), and an improvement by at least 1 point on the MHGS in both hands, and hand function tests, in particular incidence of a significant MHQ change[7] or report(s) of severe difficulty performing activities with the hand(s) or severe loss of sensation in the hand(s) since previous visit. The definition of a significant MHQ change are defined for this study as score changes of 11 for pain and 13 for function domain. These values are equivalent to the published data for rheumatoid arthritis patients.

Incidence of AEs over time will be analyzed via Kaplan-Meier time to event analyses. Event duration, severity, and incidence of recurrence will be analyzed. A particular focus will be the time to event for any AE not previously observed in the pre-market study.

Repeated measures models for the percentage of subjects experiencing events over time may be explored to characterize time trends. These will be based on logistic regression models fit via generalized estimating equations with a repeated term for subjects to account for correlation. Repeated measures models may also be employed for continuous measures, again with repeated terms for subjects to account for correlation.

Subgroup analyses will be performed for the primary efficacy and safety endpoints. Outcomes by MHGS group (A versus B) will be analyzed further by age (<60 years versus ≥ 60 years) by Fitzpatrick skin type (Grades I, II, and III versus Grades IV, V, or

[7] Shauver et al, "The Minimal Clinically Important Difference of the Michigan Hand Outcomes Questionnaire," Journal of Hand Surgery, March 2009, 34A:509-514.

VI), by initial and repeat injection volumes, and by study site by injection volume. In these analyses, subjects will be dichotomized based on injection volume less than or greater than or equal to the median injection volume. This will be done by hand (initial total injection volume per hand) and by subject (initial total injection volume by subject). Injection volumes will be recorded separately for the right hand and the left hand of each subject in the CRF for each treatment administered.

Subgroup analyses will be based on logistic regression models for the primary endpoints as a function of the subgroups, and with the appropriate interaction term. For example, for models comparing the MHGS groups by subgroup, model terms will include the MHGS group, subgroup term, and a term for the interaction of MHGS group and subgroup. Similarly, for the analysis of study site by injection volume, model terms will include MHGS group, study site, dichotomized injection volume, and the corresponding two and three way interaction terms. Analyses by hand will be based on generalized estimating equation models to account for correlations. A p-value of less than 0.05 for the appropriate interaction term will be considered statistically significant. Any such finding will result in additional exploratory analyses to understand possible causes and the clinical significance

Data from the baseline MHGS4 and baseline MHGS2-3 groups will be analyzed separately and in aggregate via descriptive statistics in addition to the above hypothesis test, with appropriate treatment of the follow-up time of each group.

[redacted]
Frequency tables (counts and percentages) and their confidence intervals (based on the binomial distribution) will be presented.

Hand function data will be summarized descriptively and compared to baseline. Hand function data will be evaluated in relation to [redacted] eport(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 2 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]

12.4.3 Other statistical/analytical issues

12.4.3.1 Discontinuations and missing data

Missing 3-month MHGS data will be imputed as no change.

13 DATA HANDLING AND RECORDKEEPING

By signing and dating the CRF, or electronic signature of the electronic case report form (eCRF) if an Electronic Data Capture (EDC) system is used, the investigator will confirm that all investigations have been completed and conducted in compliance with the clinical study protocol, and that reliable and complete data have been entered into the CRF.

All data required by this clinical study protocol are to be recorded on CRFs, or eCRFs, as soon as possible. If paper-based, entries on the CRF must be legible and made with a blue or black ballpoint pen: pencils are not permitted. The monitor is not allowed to make entries into CRF or eCRF.

For paper-based CRFs, it is not permitted to erase, overwrite, or use correction fluid or tape on the CRF. If corrections are necessary, an authorized member of the investigator's staff will enter them in the following manner: the wrong entry will be crossed out with a single line (although it must remain legible) and the correct entry will be placed next to it. Corrections will be initialed, dated, and (if necessary) explained (e.g., corrections concerning AEs or the primary variable). Corrections that become necessary after collection of original CRF data sheets have to be documented on Data Clarification Forms (DCFs) and signed by the principal investigator (PI).

All data required by this clinical study protocol are to be entered into an EDC system if applicable, and a validated database, which applies to both paper-based and EDC systems.

If corrections in the subject diary or subject MHQ are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date and initial the correction. The investigator should not make any changes to these documents.

Essential documents at the investigational site include but are not limited to:

(1) Subject files

(2) Subject identification code list

(3) A copy of the study protocol and any amendments

(4) Investigator's copies of the CRFs, DCFs forms, and any associated subject-related source data

(5) Signed ICFs

(6) Copies of all direct correspondence with the IRB and with the regulatory authority(ies), and with the Sponsor

(7) Copies of hand photographs

(8) Copies of IP disposition records

Essential documents should be retained per applicable regulations and as instructed by the study Sponsor. Study documents may not be destroyed by study site personnel prior to the end of the required retention period of 25 years. The PI or the institution must inform the Sponsor in due time if the PI leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

14 PUBLICATION POLICY

The publication policy will be in accordance with the investigator agreement with the PI as executed prior to initiation of the investigational site.

15 REFERENCES

1. Carruthers, et al., "A Validated Hand Grading Scale," Dermatol Surg 2008, 34:S179-S183.

2. Narins R, et al., "A randomized, double blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds," Dermatol Surg, 2003; 29:6.

3. Aaron DH and Jansen CWS, "Development of the Functional Dexterity Test (FDT): Construction, Validity, Reliability, and Normative Data," J Hand Ther 2003; 16: 12-21.

4. Mathiowetz V, et al., "Reliability and Validity of grip and pinch strength evaluations," J Hand Surg 1984; 9A: 222-6.

5. Mathiowetz V, et al., "Grip and pinch strength: Normative data for adults," Arch Phys Med Rehabil 1985; 66: 69-72.