Radiesse® Post Approval Safety Study - Radiological Evaluation of Implantation in the Hands

Development phase:	Device Post-market
Study protocol number:	P151010
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
Date:	13/DEC/2016 (Amendment #1)
Replaces Protocol Version:	06/JAN/2016
Primary Authors(s):	[redacted], Clinical Project Director [redacted], Biostatistician

[redacted], Merz North America Research & Development — Signature — Date

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List of Abbreviations

AE	Adverse event/effect
CRF	Case Report Form
DCF	Data Clarification Form
e-CRF	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
IFU	Instructions for use
IP	Investigational product
IRB	Institutional Review Board
MD	Medical Doctor
MHGS	Merz Hand Grading Scale
MHQ	Michigan Hand Outcomes Questionnaire
MCID	Minimal Clinically Important Difference
PI	Principal investigator
PAS	Post approval study
PMA	Pre-Market Approval
PMA-S	Pre-Market Approval Supplement
ROM	Range of Motion
SAE	Serious adverse event
USADE	Unanticipated serious adverse device effect
USP	United States Pharmacopeia
X-rays	Plain X-ray radiography images

1 SYNOPSIS

Study title

Radiesse® Post Approval Safety Study - Radiological Evaluation of Implantation in the Hands

Study phase

Device Post-Market

Study Product

Radiesse Injectable Implant

Indication

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

Primary study objective

The objective of this study is to provide a preliminary assessment of the radiographic appearance of Radiesse material that has been injected into the dorsum of the hands. The assessment will be with standard, plain radiography (X-rays). The hypothesis is that the radiographic appearance of Radiesse in the hands does not obscure the bones of the hands as seen on plain X-rays of the hand.

Primary study endpoint

The primary endpoint is the safety assessment of the incidence of obscuration of the bones of the hand at 1-, 6-, 12-, and 24-months following injection of Radiesse in the dorsum of the hand.

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

The study will enroll 20 qualifying subjects at least 22 years of age with moderate to very severe volume loss in the dorsum of their hands based on the Merz Hand Grading Scale (MHGS[1], **Figure 1**), 10 with moderate to severe volume loss (MHGS grades 2 and 3) and 10 with very severe volume loss (MHGS grade 4). Key exclusion criteria include hands with 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 adverse events (AEs). See Section 7 for the full list of inclusion and exclusion criteria.

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

Study design

This is a prospective, descriptive study designed to evaluate whether Radiesse interferes with radiological assessment by obscuring the bones of the hand.

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 after baseline X-rays, and will have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up. The retreatment interval is every six months as agreed upon by the treating investigator and the subject.

Total number of subjects and number of countries

There will be 20 subjects enrolled and treated in the United States.

Number of study sites

This will be a single-site study.

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)/ethics committee: 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.

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 ICFs must be retained at the study site; and a copy of the signed and dated written informed consent must be given to the subject or subject's legally authorized representative(s).

4 INTRODUCTION

4.1 Study background

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.

4.2 Study rationale

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[2]. 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.

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). 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 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.

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. A potential risk of participation in this study would be the potential obscuring of hand bones in X-ray images that might be taken in the event of a hand injury. For complete safety and risk information, see the Instructions For Use (IFU, **Appendix A**).

[2] Carruthers A, et. al., "Radiographic and computed tomographic studies of calcium hydroxylapatite for treatment of HIV-associated facial lipoatrophy and correction of nasolabial folds," Dermatol Surg 2008, 34:S78-S84.

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.

Potential risks associated with X-ray imaging of the hand are those that are associated with the use of X-ray imaging, that include development of cancer later in life and tissue effects such as skin reddening and hair loss. The levels of ionizing radiation and duration of exposure to be used in this study are low and are not expected to result in tissue effects.

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 1 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 the study is to provide a preliminary 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[3], 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]

5.2 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 secondary endpoints of the study are:

- MHGS at 1- and 6-months after initial treatment
- MHGS at 1- and 6-months follow retreatment for those receiving retreatment
- GAIS at 1- and 6-months after initial treatment
- GAIS at 1- and 6-months follow retreatment for those receiving retreatment
- MHQ at baseline, study exit, and other collected time points
- The rate of device/injection-related severe AEs at 1- and 6-months

[redacted]

[3] Carruthers et al, "Radiographic and computed tomographic studies of calcium hydroxylapatite for treatment of HIV-associated facial lipoatrophy and correction of nasolabial folds," Dermatol Surg 2008, 34:S78-S84.

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

[redacted]

Figure 1. Merz Hand Grading Scale (MHGS).

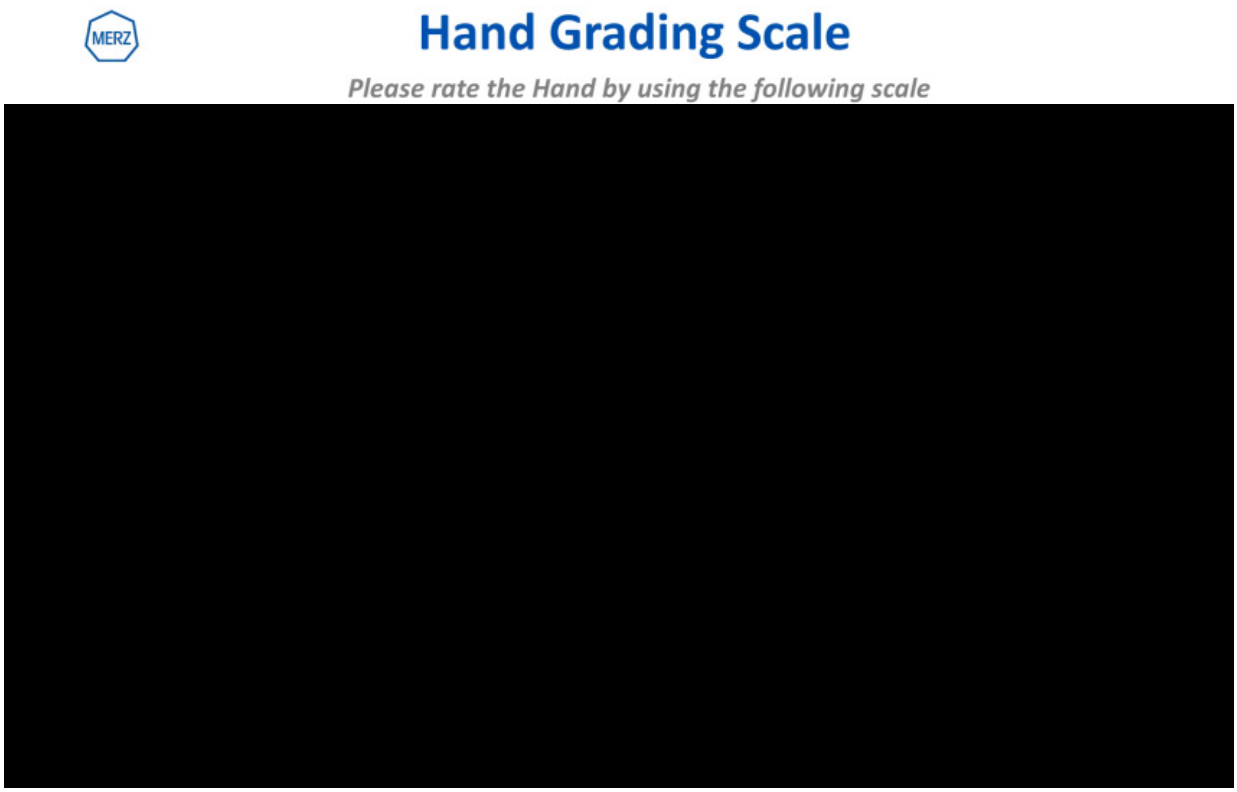


Table 1. Global Aesthetic Improvement Scale (GAIS).

RATING	DESCRIPTION
Very Much Improved	Optimal cosmetic result for the implant in this patient
Much Improved	Marked improvement in appearance from initial condition, but not completely optimal for this patient
Improved	Obvious improvement in appearance from the initial condition
No Change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition
Much Worse	Marked worsening in appearance from the initial condition
Very Much Worse	Obvious worsening in appearance from the initial condition

6 INVESTIGATIONAL PLAN

6.1 Overall 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.

Multiple assessments will be performed at study visits. 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 (**Figure 1**)– a single blinded site evaluator will grade the hands using the MHGS
- [redacted]
- MHQ – subjects will self-report assessment of the effect(s) of Radiesse injection on hand function using the MHQ
- 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
- Photographs – at baseline and exit from the study, and during the study to document a serious or medically concerning adverse event in the hands.

6.1.1 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.

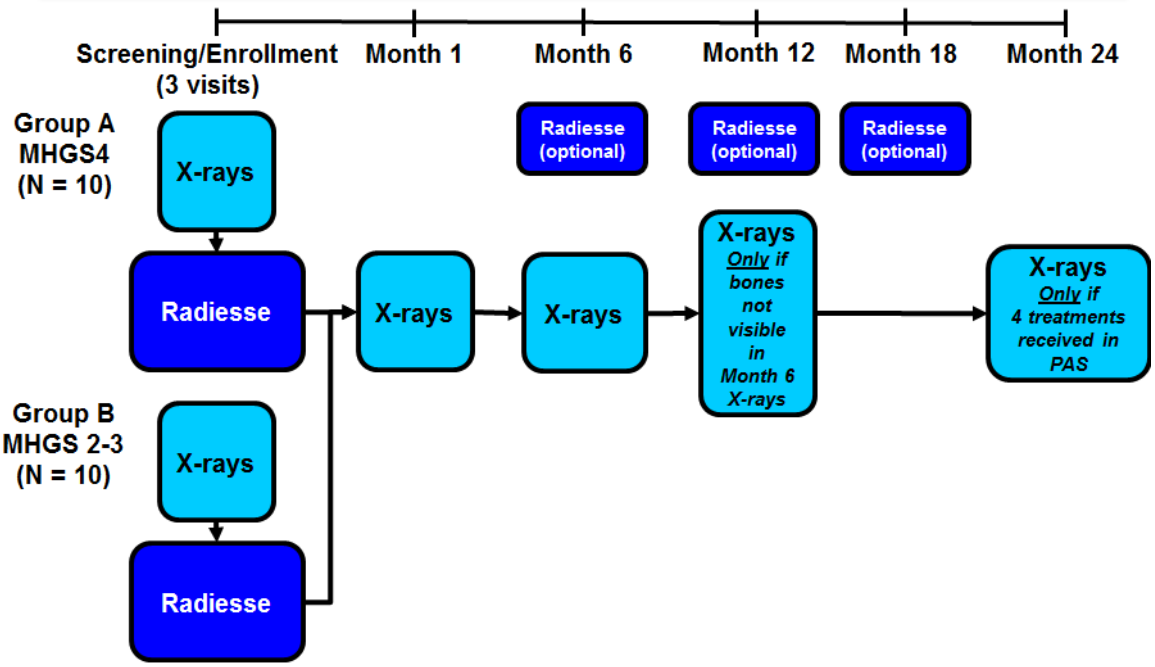
6.1.2 End of study

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 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.

6.1.3 Study flow chart

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.



6.1.4 Study timeline

Milestone	Relative to date of FDA Approval
Expected date of study initiation (First subject enrolled)	3 months
Expected monthly number of study sites with IRB approvals	N/A
Expected number of subjects enrolled per month	15
Expected date for completion of subject enrollment (Last subject, first visit)	5 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	29 months
Expected date for submission of final report	32 months

7 STUDY POPULATION

The study will enroll adults at least 22 years of age. There will be 2 study groups, with 10 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 as determined by the investigator based on the MHGS. Group A subjects will provide radiographic assessment images 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 and pre-screen candidates 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/or 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.

3. Is at least 22 years of age.[5]

4. Has signed an ICF.

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

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

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 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[6] and not using medically effective[7] birth control or is pregnant or lactating.

11. Has any other medical condition with the potential to interfere with the study or increase the risk of adverse events, such as: autoimmune disease affecting the hand,

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

[7] 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.

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 volunteer to discontinue or withdraw 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.
- 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 to 27 gauge Inner Diameter needle. The same size needle should be utilized throughout the trial for an individual subject.

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 this 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 will be dispensed a 30-day take-home diary on which to record AEs that may occur before their next visit (**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:

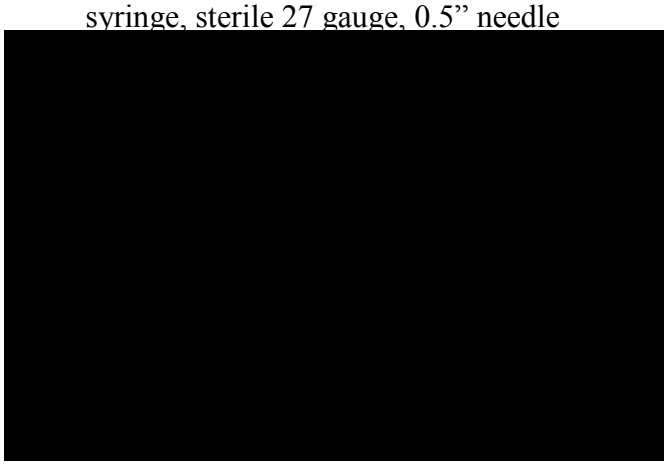
- Radiesse injectable implant syringe(s) – 1.5cc
- Sterile 27 gauge, 0.5" regular-wall needle with luer lock connector
- 3.0cc sterile polypropylene luer lock syringe [redacted]
- 0.2cc of [redacted] 2% lidocaine HCl for injection, USP solution (not supplied by Merz North America, Inc.)
- Sterile female-to-female 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 North America, Inc. 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 0.26cc 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. 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, 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.

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

[redacted] Subjective functional outcomes will also be assessed at baseline and at 1-, 3-, 6-, 7-, 12-, 13-, 18-, 19- and 24-months following initial injection of Radiesse using the validated MHQ (**Appendix C**). The MHQ is a patient-rated outcome tool based on psychometric principles that is capable of measuring health status domains that are important to patients with hand disorders. [redacted]

[redacted]

9.1.4 Evaluation of hand X-rays

X-rays will be taken at a licensed radiographic imaging center. Plain anteroposterior and lateral views (**Figure 7**) of each hand will be taken at each required study timepoint. Digitized radiographic images will be transmitted to the imaging core lab to be assessed by 2 blinded, licensed radiologists. Copies of digitized X-rays will be sent from the imaging center to the investigational site and the Sponsor. The core lab will send confirmation of completed X-ray assessments to the investigational site and the Sponsor. The core lab will send results of the X-ray assessments to both the site and Sponsor within 21 days of receiving the digital X-rays from the imaging center. Results of the 6-month X-ray assessments will be used to determine the need to schedule X-rays prior to

the 12-month in-office follow-up visit. After completion of all 18-month follow-up visits at the site, both the local licensed imaging center and core lab will be informed of the total number of subjects who will be scheduled for 24-month X-rays. Only subjects who receive a total of 4 Radiesse hand treatments (initial, 6-, 12-, and 18-month treatments) will be required to have X-rays of their hands prior to the final study visit at 24-months.

Figure 7. Plain X-rays of the left hand showing a long oblique fracture of the 2nd metacarpal. *The hand was not implanted with Radiesse.*
A = anteroposterior view, B = lateral view.

The core lab radiologists will remain blinded to the study design, including any study timepoints that might involve Radiesse hand treatment. Timepoints will be listed by number of months from enrollment, and will not include any unblinding descriptors (e.g., injection visit). Further, the core lab radiologists will be asked to compare the prominence of any foreign material to that of the previous x-ray for that subject (where applicable). Consequently, documentation of the study timepoint associated with the x-ray image being read does not impact the integrity of the data reported by the core lab radiologists.

9.2 Visit schedule

Screening and Enrollment

Enrollment will be limited to 20 subjects for the study. The Sponsor will oversee enrollment and be in direct communication with the investigational site to make all efforts not to exceed the enrollment target of 20 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. If it is determined that a presenting subject meets these selection criteria, the subject will be given an Informed Consent Form to review and sign.

There will be 3 visits during the screening and enrollment period: 2 at the investigational site, and 1 at the local X-ray imaging center. The X-ray visit may be performed on the same day as the consent or injection.

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 (XR = X-Ray), site identification number, and subject enrollment order number. For example, the third subject enrolled will receive study ID number XR-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. Study information including demographics and concomitant medications will be recorded, and photographs will be taken of each hand. The subject will then be scheduled for hand X-rays to be taken prior to Radiesse hand treatment.

Within 72 hours after enrollment: Subjects will have X-rays taken of their hands at a designated, local, licensed imaging center.

Week 1/Initial treatment visit: 7 ± 6 days from enrollment, all subjects will return for a follow-up visit after completing the corresponding X-ray visit to the designated imaging center. This visit can be scheduled on the same day as the X-ray visit. Females of childbearing age will complete a urine pregnancy test. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subjects will complete the MHQ [redacted]. 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. Photographs of the hands will be taken only in the event of a serious or medically concerning AE. Subjects will be scheduled for the Month 1 X-ray and follow-up visits.

Follow-Up Evaluations

72 hours after Week 1/initial treatment: Subjects 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 1 X-rays: 30 ± 5 days from enrollment, all subjects will have x-rays taken of their hands at a designated, local, licensed imaging center. This visit must be completed prior to the Month 1 follow-up visit at the investigational site.

Month 1: 30 ± 5 days from initial treatment, all subjects will return for a follow-up visit after completing the corresponding X-ray visit to the designated imaging center. Changes in concomitant medications will be recorded by the study staff. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] A physician will assess the subject's hands for AEs. 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 only in the event of a serious or medically concerning AE.

Month 6 X-rays: 180 ± 10 days from enrollment, all subjects will have X-rays taken of their hands at a designated, local, licensed imaging center. =This visit must be completed prior to the Month 6 follow-up visit at the investigational site.

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. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] A physician will assess the subject's hands for AEs. A urine pregnancy test will be completed for female subjects of child bearing potential. A Radiesse retreatment will be performed on both hands if agreed upon by treating investigator and subject. A take-home 30-day diary will be given to the subject if a retreatment is received. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

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 adverse events. Subjects will be reminded to continue daily entries into their 30-day diary.

Month 7: 210 days ± 5days from enrollment, only subjects who received a retreatment at Month 6 will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] A physician will assess the subject's hands for AEs. The take-home 30-day diary will be reviewed for completion and collected. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 12 X-rays: 360 ± 10 days from enrollment, only subjects whose hand bones were not visible in the Month 6 X-rays will have X-rays taken of their hands at a designated, local, licensed imaging center. This visit must be completed prior to the Month 12 follow-up visit at the investigational site.

Month 12: 360 ± 10 days from enrollment, all subjects will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] A physician will assess the subject's hands for AEs. A urine pregnancy test will be completed for female subjects of child bearing potential. A Radiesse retreatment will be performed on both hands if

agreed upon by treating investigator and subject. A take-home 30-day diary will be given to the subject if a retreatment is received. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

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 days ± 5 days from enrollment, only subjects who received a retreatment at Month 12 will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] A physician will assess the subject's hands for AEs. The take-home 30-day diary will be reviewed for completion and collected. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 18: 540 ± 10 days from enrollment, all subjects will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] A physician will assess the subject's hands for AEs. A urine pregnancy test will be completed for female subjects of child bearing potential. A Radiesse retreatment will be performed on both hands if agreed upon by treating investigator and subject. A take-home 30-day diary will be given to the subject if a retreatment is received. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

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 days ± 5 days from enrollment, only subjects who received a retreatment at Month 18 will return for a follow-up visit. Changes in concomitant medications will be recorded by the study staff. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ. [redacted] physician will assess the subject's hands for AEs. The take-home 30-day diary will be reviewed for completion and collected. Photographs of the hands will be taken only in the event of a serious or medically concerning AE.

Month 24 X-rays: 720 ± 30 days from enrollment, only subjects receiving a total of 4 treatments (initial, 6-, 12, and 18-months) will have X-rays taken of their hands at a

designated, local, licensed imaging center. This visit must be completed prior to the Month 24 follow-up visit at the investigational site.

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. The subject's hands will be assessed on the MHGS by a live, masked evaluator. Subject self-assessment of aesthetic improvement will be performed using the GAIS. Subjects will complete the MHQ [redacted]. A urine pregnancy test will be completed for female subjects of child bearing potential. A physician will assess the subject's hands for AEs. Photographs of the hands will be taken. 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, the subject will complete an MHQ, and photographs of the hands will be taken.

Table 2. Schedule of Events.

Assessment	Screen-ing/ Enroll-ment	X-ray Wk 1	Wk 1†	Mo 1	X-ray Mo 6	Mo 6	Mo 7**	X-ray‡ Mo 12	Mo 12	Mo 13**	Mo 18	Mo 19**	X-ray* Mo 24	Mo 24
Visit Window (Day)	-7 to 0	Day 3 +- 3	Day 7 +0-7	Day 30 +-5	Day 180 +-10	Day 180 +-10	Day 210 +-5	Day 360 +-10	Day 360 +-10	Day 390 +-5	Day 540 +-10	Day 570 +-5	Day 720 +-30	Day 720 +-30
Inclusion/ Exclusion	X													
Informed Consent	X													
Demographics	X													
Concomitant Medications	X			X		X	X		X	X	X	X		X
Merz Hand Grading Scale – Masked Evaluator	X			X		X	X		X	X	X	X		X
Michigan Hand Outcome Questionnaire			X	X		X	X		X	X	X	X		X
[redacted]														
Subject GAIS				X		X	X		X	X	X	X		X
Urine Pregnancy Test	Xα		Xα			Xα			Xα		Xα			Xα
X-rays of Hands		X		X††	X††			X‡					X*	
Hand Treatment			X			Xᵞ			Xᵞ		Xᵞ			
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
Hand Photographs	X		X‡‡	X‡‡		X‡‡	X‡‡		X‡‡	X‡‡	X‡‡	X‡‡		X

† To be scheduled after Week 1 X-ray, and can be on the same day after X-rays are taken
†† Corresponding X-ray imaging center visit must be completed prior to investigational site visit
* To be scheduled only for subjects receiving 4 treatments (enrollment, Months 6, 12, and 18)
** Only if repeat treatment received
‡ To be scheduled only if bones of at least 1 hand are not visible on Month 6 X-rays
‡‡ Only to document a serious or medically concerning adverse event
ᵞ Only if treatment is indicated as agreed upon by investigator and subject
[redacted]
α Prior to X-ray or Radiesse treatment

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 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.[8]

(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.[9]

All SAEs that occur during the study period, whether considered to be related to the IP or not, must be reported by e-fax within 24 hours of knowledge of the event.

Please fax completed SAE forms to:

Product Safety Department
Merz North America, Inc.
6501 Six Forks Road
Raleigh, North Carolina 27615
e-fax: **1-336-458-5983**

[8] 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.

[9] 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), 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

Given that the study is a radiologic evaluation to obtain a preliminary assessment, the planned sample size is not based on power calculations for a formal statistical hypothesis test, but rather is 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 to radiation.

12.2 Analysis sets

Analyses will be based on all enrolled subjects with available data. The primary event of interest, and primary endpoint of the study, is whether treatment with Radiesse interferes with radiological assessment by obscuring the bones of the hand at any time during the study. Obscuration is defined as any hand X-ray that at least 1 of the 2 blinded imaging core lab radiologists interprets as Radiesse obscuring bones. This will be based on assessments performed post-treatment. 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. No formal hypothesis tests are planned but nominal results from tests may be reported based on exploratory analyses.

12.3 Variables for analysis

12.3.1 Primary safety variable

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.

12.3.2 Secondary efficacy and safety variables

The secondary efficacy and safety 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 follow 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 follow retreatment for those receiving retreatment
- MHQ scores at baseline, study exit, and other collected time points. The rate of device/injection-related severe AEs at 1- and 6-months

12.3.3 Other efficacy and safety variables

Other efficacy and safety variables are as follows:

- MHGS at 12-, 18-, and 24-months after initial treatment
- MHGS at 12- and 18-months follow retreatment for those receiving retreatment
- GAIS at 12-, 18-, and 24-months after initial treatment
- GAIS at 12- and 18-months follow retreatment for those receiving retreatment
- The rate of device/injection-related severe adverse events at 12-, 18- and 24-months
- Incidence of all AEs over the course of the study
- [redacted]

12.4 Statistical analysis methods

12.4.1 Primary safety variable

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. No formal hypothesis tests are planned but nominal results from tests may be reported based on exploratory analyses.

12.4.2 Secondary and other efficacy and safety variables

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 percent of subjects with both hands improved. Groups A and B will be analyzed separately and in aggregate. Confidence intervals will be based on a 5% nominal alpha level.

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.

Descriptive statistics will be provided for the MHQ at baseline, study exit, and other collected time points. [redacted]

12.4.3 Other statistical/analytical issues

12.4.3.1 Discontinuations and missing data

Missing 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 a paper-based 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, 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 A, et. al., "Radiographic and computed tomographic studies of calcium hydroxylapatite for treatment of HIV-associated facial lipoatrophy and correction of nasolabial folds," Dermatol Surg 2008, 34:S78-S84.

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16 APPENDICES

Appendix A Radiesse Instructions for Use

Appendix B 30-day Subject Diary (Sample)

Appendix C Michigan Hand Outcomes Questionnaire (MHQ)

Appendix D Informed Consent Form Template

Appendix E [redacted]

Appendix F Case Report Forms

Statement of Compliance

Investigational Site

I have thoroughly read and reviewed the clinical study protocol. Having understood the requirements and conditions of the clinical study protocol, I agree to perform the clinical study according to the clinical study protocol, the CRF, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.

I have received the current summary of product characteristics. Having been adequately informed about the IP development to date, I also agree to:

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received approval from the appropriate Independent Ethics Committee (IEC)/ Institutional Review Board (IRB before enrolling any subject in this study.
- Obtain informed consent for all subjects prior to any study-related action performed.
- Start the study only after all legal requirements in my country have been fulfilled.
- Permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections.
- Provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, IEC/IRB, or regulatory authority upon request.
- Use the IP and all study materials only as specified in the clinical study protocol.
- Report to Merz and/or IEC/IRB as required, within 24 hours of discovery, any AE that is serious, whether considered treatment related or not.
- Prior to initiating the study, I will provide the sponsor with a written disclosure of any financial interest in accordance with 21 CFR Part 54.

Furthermore, I understand that:

- Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of Merz and – as applicable – of the appropriate IEC/IRB and regulatory authority.
- The content of the clinical study protocol is confidential and proprietary to Merz.
- Any deviation from the clinical study protocol may lead to early termination of the study site.

Principal investigator (PI) (Print name)	Date	PI Signature