Evaluation of the Effectiveness and Safety of Radiesse for the Correction of Nasolabial Folds

Development phase:	Device Pre-market in China
Study protocol number:	M900311004
Name of medical device:	RADIESSE®
Generic name:	Radiesse Injectable Implant
Specification:	1.5mL/Syringe
Indication/intended use:	Correction of the moderate to severe nasolabial folds (NLFs)
Management category of the clinical medical device:	Class III Medical Device to conduct examination and approval of the clinical trial **Yes**☐ **No**☒ Similar Products in China **Yes**☐ **No**☒
Clinical Trial Site	Nanfang Hospital Southern Medical University
Investigational (s):	[redacted] Department of Aesthetic Plastic Surgery, Nanfang Hospital Southern Medical University
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Amendment/Date:	Amendment 1, 17/Mar/2017 Amendment 2, 19/Sep/2017 Amendment 3, 27/Jul/2018

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[redacted] Global Clinical Operations <Signature > <Date>

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
ATC	Anatomical Therapeutic Chemical
BDDE	Butanediol Diglycidyl Ether
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CaHA	Calcium Hydroxylapatite
CFDA	Chinese Food and Drug Administration
CI	Confidence Interval
CMDE	Center of Medical Device Evaluation
CRO	Contract Research Organization
CSR	Clinical Study Report
DHPV	Drug Safety and Pharmacovigilance
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEWR	Familywise Error Rate
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic acid
IEC	Independent Ethics Committee
I.D.	Inner Diameter
IB	Investigator Brochure
ICF	Informed Consent form
ICH	International Conference on Harmonization
IFU	Instructions for Use
IP	Investigational Product
IWRS	Interactive Web Response System
LIS	Liquid Injectable Silicone

MedDRA	Medical Dictionary for Regulatory Activities
NLFs	Nasolabial Folds
PD	Protocol Deviation
PI	Principal Investigator
PMMA	Polymethyl-methacrylate
PPS	Per Protocol Set
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plans
SES	Safety Evaluation Set
SOP	Standard Operation Procedure
TEAE	Treatment Emergent Adverse Event
USADE	Unanticipated Serious Adverse Device Effect
USP	United States Pharmacopeia
WHODD	World Health Organization Drug Dictionary
WSRS	Wrinkle Severity Rating Scale

1 SYNOPSIS

Study title

Evaluation of the Effectiveness and Safety of Radiesse for Nasolabial Folds

Study phase

Device Pre-market in China

Study products

RADIESSE® or Radiesse® （Generic name: Radiesse Injectable Implant）

Restylane®

Indication

Correction of the moderate to severe nasolabial folds (NLFs)

Study objectives

The objectives of this study are to evaluate the effectiveness and safety of Radiesse for the correction of nasolabial folds (NLFs).

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

This trial will enroll Chinese adult subjects who have NLFs with moderate or severe grade of 3 or 4 on Wrinkle Severity Rating Scale (WSRS). Both folds must have the same NLF score to qualify for entry into the study.

Main criteria

Inclusion criteria

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

1. Is 22 - 65 years of age.
2. Has symmetrical NLFs of moderate or severe intensity (grade 3 or 4) on the WSRS as determined by the independent blinded evaluator and confirmed by the treating investigator at baseline.
3. Both folds must have the same NLF score at baseline.
4. Has signed an informed consent.

5. Understands and accepts the obligation not to receive any other facial procedures below the eyes during the study.
6. Understands and accepts the obligation to present for all scheduled follow-up visits and is logistically able to meet all study requirements.
7. Subjects of childbearing potential must have a negative pregnancy test result and must not be lactating at the Screening/Baseline Visit and be willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study. Women will be considered if one of the following conditions is documented on the medical history:
    a. Postmenopausal with last menstrual bleeding at least 12 months prior to study; and
    b. Without a uterus and/or both ovaries.

Exclusion criteria

Subjects must not meet any of the following exclusion criteria:

1. Has received surgical permanent implants, grafting, or surgery below the eyes on the face prior to injection or lower lid blepharoplasty within 6 months prior to injection.
2. Has received within the specified (washout) period or plans to receive treatment during the study conduct with a non-permanent facial filler in any facial area below the eyes:
    a) 12 months prior to study start - hyaluronic acid [HA] or collagen
    b) 18 months prior to study start - calcium hydroxylapatite [CaHA]
3. Has received at any time or plans to receive during the study a permanent facial filler (e.g. poly L-lactic acid [PLLA], polymethyl-methacrylate [PMMA], silicone) below the eyes.
4. Has received within the past 6 months or plans to receive during the study facial dermal resurfacing procedures (e.g. chemical peel, dermabrasion, ablative laser resurfacing), non-invasive skin-tightening (e.g. Thermage), botulinum toxin injections, mesotherapy, or fat injections below the eyes.
5. Has received in the past 2 weeks or plans to receive during the study any prescription wrinkle therapies (e.g. RENOVAÒ), topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) for use on the face.
6. Has received in the past 2 months, or plans to receive immunosuppressive medications or systemic steroids (intranasal/inhaled steroids acceptable) during the study.

7. Has an acute inflammatory process or infection, active herpes infection, or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of adverse events (AEs).
8. Has a known bleeding disorder or has received or is planning to receive anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs (e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko), from 10 days before injection to 3 days after injection.
9. Has a history of known liver or renal function disease/disorder or has clinically significant laboratory values at baseline.
10. Has a known history of allergic/anaphylactic reactions, including hypersensitivity to lidocaine or anesthetics of the amide type, or any of the device components.
11. Has a history of hyper- or hypo-pigmentation in the NLFs, keloid formation, or hypertrophic scarring.
12. Has recently lost or has the intention to lose a significant amount of weight ≥ 2 Body Mass Index (BMI) units] during the course of the study.
13. Has any other medical condition with the potential to interfere with the study's conduct or assessments, or increase the risk of AEs.
14. Has participated in a study in the last 30 days or is enrolled or plans to enroll in any other interfering investigational study during participation in the study.
15. Is an employee or direct relative of an employee of the investigational department in site or the sponsor.

Study design

The planned study is a 12-month, multicenter, non-inferiority, split-face, active comparator, randomized, blinded (evaluator and subject) study evaluating the effectiveness and safety of Radiesse versus Restylane for the correction of NLFs in adult subjects. Subjects will have the option of a touch-up injection in one or both NLFs 4 weeks after the initial injection. Approximately 174 subjects will be enrolled into the study. During the baseline visit, for each subject, one NLF will be randomized to be treated with Radiesse and the other with Restylane. Subjects will be enrolled at approximately 4 investigational sites in China.

Planned study period

The planned study period is 12 months consisting of the following visits:

- Visit 1 (Screening): Screening and Baseline Visits may be the same day
- Visit 2 (Baseline/Treatment): Day 1, Injection

- Visit 3 (Week 4 / 1 month Post Treatment): Optional touch-up with the same randomized product
- Visit 4 (3 months Post Treatment)
- Visit 5 (6 months Post Treatment)
- Visit 6 (9 months Post Treatment)
- Visit 7 (12 months Post Treatment)

Duration of treatment per subject

Subject's NLFs will be treated with an initial injection of Radiesse on one side of the face and Restylane on the other side of the face with an optional touch-up injection 4 weeks after initial treatment in order to achieve optimal correction.

Total number of subjects and number of countries

Approximately 174 subjects will be enrolled in China.

Number of study sites

Subjects will be enrolled at approximately 4 investigational sites in China.

2 STUDY ADMINISTRATIVE STRUCTURE

INVESTIGATOR AND PARTICIPANT

Clinical trial institution code	Clinical trial institution name	Investigator	Title	Contact information
0860006	Nanfang Hospital Southern Medical University	[redacted]	[redacted]	[redacted]
0860003	Peking University First Hospital	[redacted]	[redacted]	[redacted]
0860005	Zhejiang Provincial People's Hospital	[redacted]	[redacted]	[redacted]
0860007	Xiangya Hospital, Central South University	[redacted]	[redacted]	[redacted]

3 ETHICS

3.1 Independent Ethics Committee

The following documents (at a minimum) must be submitted to the responsible Ethics Committee (EC) and approval obtained:

- The clinical study protocol and any protocol amendments, if applicable.
- The investigator brochure.
- Subject information and informed consent forms.
- All subject recruitment procedures and any advertisement used to recruit subjects (if applicable).
- Any other required documents.

3.2 Ethical Conduct of the Study

This study will be conducted in accordance with all applicable regulations. It will be conducted in compliance with the clinical study protocol, International Conference of Good Clinical Practice for Medical Devices (No. 25 Order of CFDA and National Health and Family Planning Commission of the People's Republic of China (NHFPC)), Harmonization (ICH) guidelines for Good Clinical Practice (GCP) principles, the Declaration of Helsinki, and regulatory authority requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the study.

3.3 Informed Consent

Informed consent will be obtained from all study subjects prior to any procedures being conducted (see Informed Consent Form).

The consent must be confirmed by the investigator (or authorized designee) who conducted the informed consent briefings. The subject will be given a copy of the signed and dated written informed consent form as well as all consent form updates (if applicable).

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 adverse events (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.

4 INTRODUCTION

4.1 Study Background

As part of the natural aging process, and accelerated by exposure to sunlight, poor nutritional habits, smoking, genetic patterns, and other factors, over time the skin starts to lose its youthful appearance, particularly in the face. The most common signs of facial aging include visibility of bony landmarks, skin wrinkles, deep furrows, prominence of nasolabial folds, perioral vertical rhytids, ptosis of the oral commissures, and thinning of the lips[1].

Throughout recorded history, women and men have been trying to achieve and preserve a youthful appearance, and many techniques have been designed to help rejuvenate the face. These facial treatments and techniques attempt to address a subject's need for improved appearance by striving to meet the subject's – and likely a community or regional – aesthetic standard. Conventional facial rejuvenation surgery remains the treatment of choice for subject's requiring extensive aesthetic changes. However, injectable soft tissue fillers are being seen increasingly as an acceptable option for correction of certain specific signs of aging, such as deep nasolabial folds, marionette lines, buccal commissures, perioral wrinkles, and other cases in which the subject wishes to improve some particular facial feature. Over the last few years, injectable fillers have become an integral part of cosmetic therapy.

At present, dermal fillers are subcategorized into biodegradable and nonbiodegradable agents[2].

4.1.1 Nonbiodegradable Fillers

Permanent fillers, like polymethyl-methacrylate (PPMA) or liquid injectable silicone (LIS), can yield excellent, long-term results, but require injection by a skilled practitioner. Furthermore, as attributed to their longevity, late-onset complications may be more prevalent with nonbiodegradable fillers when compared to shorter-acting injectable fillers[2].

4.1.2 Biodegradable Fillers

Current biodegradable fillers stimulate neocollagenesis for more sustained aesthetic improvements. These fillers carry a low risk of adverse events or serious complications. Compared to permanent implants, most biodegradable products stimulate dermal collagen for long-lasting correction allowing for greater lift with fewer side effects[2]. Biodegradable fillers currently available worldwide include fat and collagen, hyaluronic acid (HA) products, and calcium hydroxylapatite (CaHA)[2].

4.1.2.1 *Calcium Hydroxylapatite (CaHA)*

CaHA is categorized as a biodegradable filler; it follows the same metabolic pathway as the bone debris that results from common bone fractures. Radiesse, a type of injectable, biodegradable filler, consists of [redacted] ynthetic CaHA microspheres (diameter of 25-45μm), suspended in a [redacted] queous carboxymethylcellulose gel carrier. Radiesse first received European Union (EU) approval in 2003 for plastic and reconstructive surgery, including deep dermal and subdermal soft tissue augmentation of the facial area[3]. In 2006, Radiesse received Food and Drug Administration (FDA) approval for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and/or for the correction of lipoatrophy in people with human immunodeficiency virus. Having been marketed in more than 50 countries[3], Radiesse has become a very effective filler agent, providing needed soft tissue augmentation for many areas of the face, all while maintaining a high and well-established safety profile.

4.2 Study Rationale

4.2.1 Summary of Animal Studies

Various animal studies evaluating Radiesse in dermal soft tissue augmentation have been conducted as follows[4]:

- Subdermal Filler Materials in Yucatan Mini-Pig: 28-day study

  Radiesse was injected subdermally at sites parallel to the lumbar region of the vertebral column. At 28 days, the animals were sacrificed and the subdermal tissue was visually examined and then prepared for histological examination. No samples showed evidence of adverse tissue reactions.

- Local and Systemic Effects in Rabbits: 6-month study

  New Zealand White rabbits were injected subdermally with 0.25mL of Radiesse, Coaptite, and the gel carrier component alone (same gel carrier for both Radiesse and Coaptite). Animals were evaluated at 3 and 6 months after injection via urinalysis, hematology, clinical chemistry, macroscopic observations, general health, and histological evaluation. All animals were normal macroscopically, with no evidence of migration or local reaction. No lymph nodes in the area draining the injection sites were enlarged or detected. None of the test articles including Radiesse showed evidence of migration, capsule formation, or adverse reactions.

- Durability and Absorption Profile in a Canine Model: 32-week study

  The study evaluated the durability and absorption profile of Radiesse when injected into the intradermal and subdermal tissues in 12 canines. Animals were sacrificed and evaluated at 4, 8, 12, 16, 24, and 32 weeks after injection. The local reactions were transient and not considered unusual for an injected dermal filler material. At 32 weeks, no erythema or edema was observed. There was no evidence of migration of Radiesse from the injection site, and the lymphatic vessels were unremarkable.

- Durability and Absorption Profile in a Yucatan Mini-Pig Model: 32-week study

The study evaluated various dermal fillers in the swine model when injected intradermally and subdermally in the Yucatan Mini-Pig. Eleven animals were injected and animals were sacrificed and evaluated at 4, 8, 12, 16, 24, and 32 weeks after injection. The local reaction scores were transient. At 32 weeks, no erythema or edema was observed in any of the test animals.

- Evaluation of Urinary Sphincter Augmentation Implantation in Dogs: 3-year study

  Radiesse was injected into the urinary bladder neck in 24 female mongrel dogs. Twelve additional female dogs were similarly injected with only the gel carrier component as the control. Blood and urine samples were collected from each animal prior to study initiation, prior to termination, and at 6-month intervals for animals through the 36-month test period. Designated animals were removed from the study at 1, 3, 6, 12, 25, and 36 months. Each was necropsied; injection sites and other tissue inspected grossly, and implant sites and selected tissues processed for microscopic examination.

  Microscopic evaluation of the implant sites at 1, 3, 6, and 12 months revealed a simple macrophage clearing response was associated with the gel carrier. The presence of the test article caused no reaction in the adjacent tissues. The CaHA particles from 1 through 36 months remained encapsulated with no evidence of migration from the injection site. The beginning of CaHA particle disintegration was present in several 25- and 36-month tissue specimens as the particles were being engulfed and solubilized 'in situ' by macrophages at the site. Many other particles remained intact.

The *in vitro* and *in vivo* (animal) studies conducted to date did not identify any specific safety signal and support the view that Radiesse is non-toxic in nature and not associated with safety concerns.

4.2.2 Summary of Clinical Studies

Pivotal trials

The pivotal clinical trial that led to the FDA approval of Radiesse for aesthetic correction of nasolabial folds was a multicenter study of 117 subjects with symmetric moderate to deep nasolabial folds. In this premarket study, subjects received Radiesse on one side of the face and human collagen on the other. Seventy-nine percent (79%) of subjects had superior improvement on the Radiesse side through 6 months ($p<0.0001$). For optimal correction, significantly less volume and fewer injections were needed for Radiesse than for collagen ($p<0.0001$). Adverse event rates were comparable, with some increase in bruising and edema for Radiesse-treated sides. Adverse event duration was similar for both groups and generally resolved within 14 to 21 days[5].

Long-Term Follow-Up

A total of 102 of the initial 117 subjects were enrolled and evaluated at intervals up to 39 months after the last injection of Radiesse. At least 30 months after the last Radiesse

treatment, 40 percent (40%) of the folds evaluated remained improved. There were no long-term or delayed-onset adverse events in subjects followed for up to 39 months, including no reports of nodules, foreign body granulomas, or infections[6].

Long-term clinical experience, clinical research, peer-reviewed publications, and regulatory approvals have demonstrated the safety and effectiveness of Radiesse[3].

A clinical trial to confirm the safety and effectiveness of Radiesse for the correction of nasolabial folds (NLFs) in Chinese adults is planned for Radiesse registration and consecutive marketing in China in accordance with appropriate Chinese laws and regulatory requirements.

4.3 Risk-benefit Assessment

4.3.1 The Analysis of Possibility of Success

Radiesse is a highly effective agent for many areas of facial soft-tissue augmentation and is associated with a well-established safety profile. Potential benefits of Radiesse include the following:

- Radiesse is currently resorbable CaHA filler on the market that immediately replenishes lost volume, while, at the same time, stimulating the production of the skin's natural collagen for long-lasting results.
- CaHA is a very effective agent for many areas of facial soft tissue augmentation and is associated with a high and well-established safety profile[3].

As described previously, Radiesse has been evaluated extensively in both US and rest of world studies. The safety and effectiveness of Radiesse therapy have been demonstrated consistently on an international scope, from clinical outcomes obtained in rigorous randomized controlled trials to worldwide commercial experience.

4.3.2 Post-Marketing Surveillance

The possibility of failure will be caused by risk or safety problems (such as severe AEs and SAEs). All these factors may lead to study termination or study failure.

The common adverse events observed after Radiesse injection included severe ecchymosis, edema, erythema, embolization and pain which may lead to subject reject the study.

And in Section 8.4, the restrictions during the study may be the possibility failure.

Nodule formation can occur after injection of Radiesse into the oral mucosa and the lips. Injection of any filler into a blood vessel may occlude the vessel and could cause infarction or embolism leading to ischemia, necrosis, or scarring; however, these latter cases are related to poor injection technique, rather than filler product.

Risks associated with the specified device are included in the Investigator Brochure (IB) and/or Instructions for Use (IFU) of Radiesse (see Appendix 1).

5 STUDY OBJECTIVES

The objectives of this study are to evaluate the effectiveness and safety of Radiesse for the correction of NLFs.

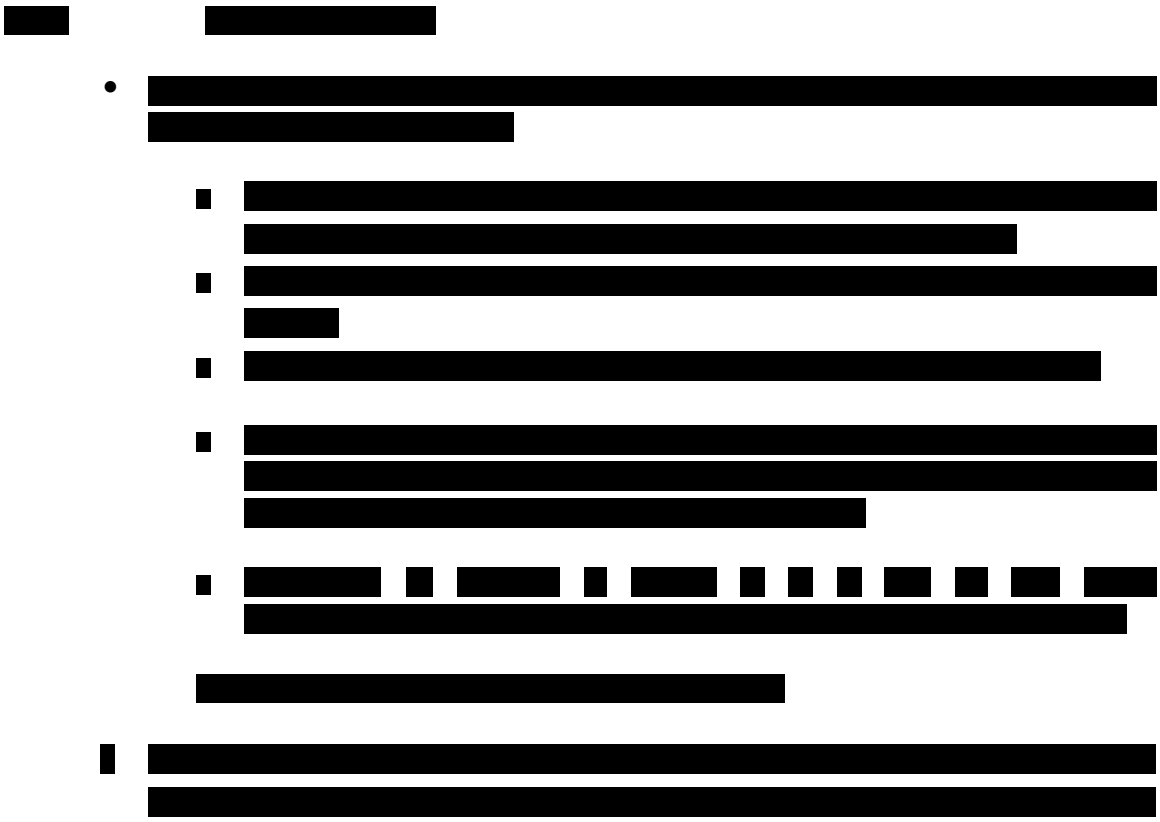
5.1 Study Endpoints

5.1.1 Primary Effectiveness Endpoint:

Compare the proportion of NLFs with treatment success in the Radiesse and Restylane groups at Month 6. Treatment success is defined as a ≥ 1-point improvement from baseline, as assessed by a blinded evaluator on a 5-point Wrinkle Severity Rating Scale (WSRS) scale[7].

5.1.2 Secondary Effectiveness Endpoint:

Compare the proportion of NLFs with an "improvement" in the blinded evaluator's Global Aesthetic Improvement Scale (GAIS) score at Month 6 between the NLFs treated with Radiesse versus Restylane. An "improvement" on the GAIS will be classified as "improved", "much improved", or "very much improved". The pre-treatment photograph will be used as a reference to assess the level of improvement at Month 6.



[redacted]

5.1.4 Safety Endpoints:

- Incidence of adverse events (AEs) including serious adverse events (SAEs), AEs related to treatment as assessed by the investigator, and AEs leading to discontinuation during the study.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

Approximately 174 Chinese subjects will be enrolled into this study. Subjects will be enrolled at approximately 4 investigational sites in China. The planned study is a 12 months, prospective, split-face, active comparator, randomized, double-blind study evaluating the effectiveness and safety of Radiesse versus Restylane for the correction of NLFs in adult subjects.

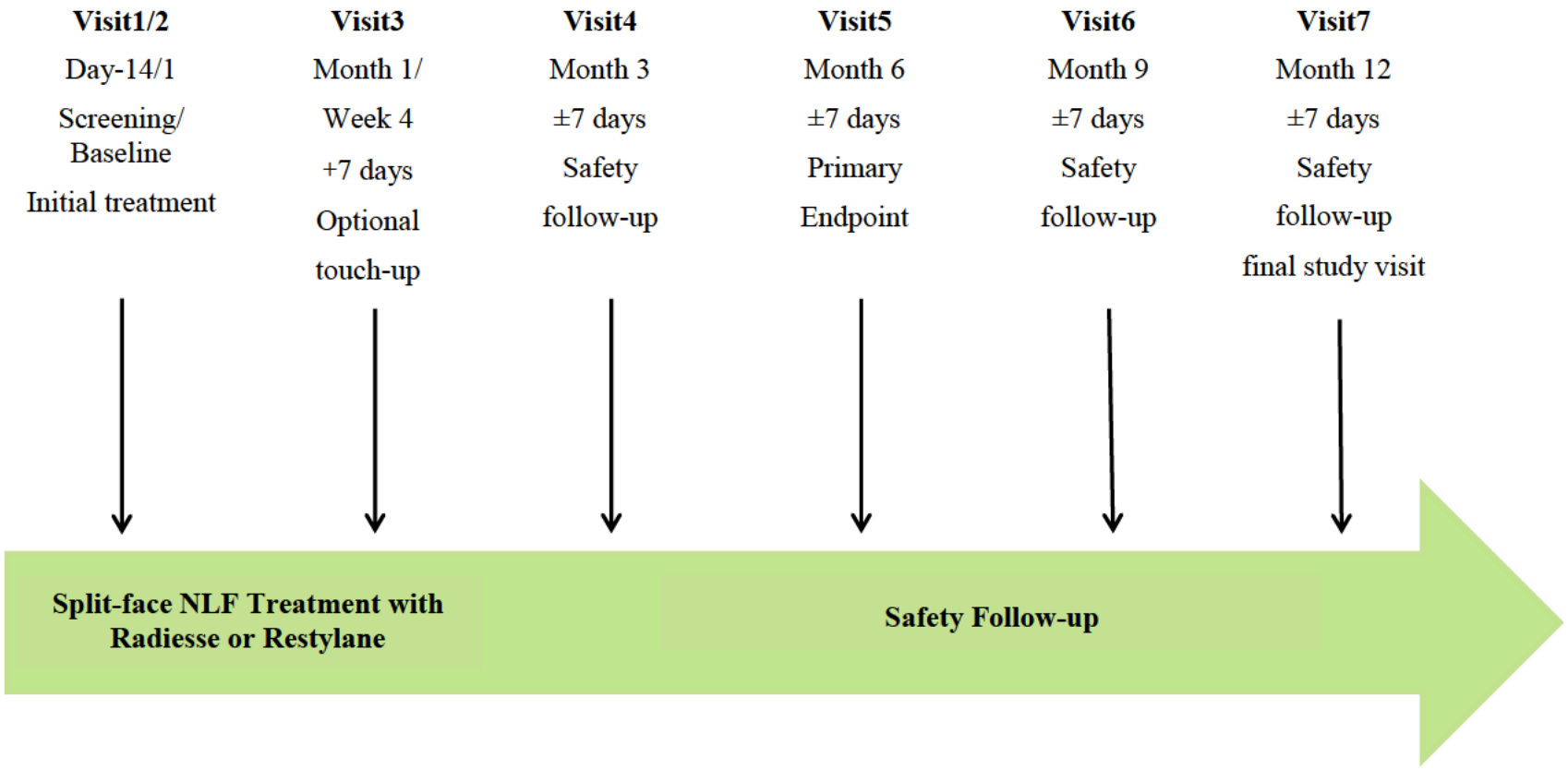
During the baseline visit for each subject, one NLF will be randomized to be treated with Radiesse and the other with Restylane. Subjects will have the option of a touch-up injection in one or both NLFs 4 weeks after the initial injection with the same randomized treatment.

6.1.1 End of Study

The end of the study is the date of the last visit of the last subject.

6.1.2 Study Flow Chart

Figure 1 Study flow chart



7 STUDY POPULATION

This trial will enroll Chinese adult subjects with NLFs with a grade of 3 or 4 on Wrinkle Severity Rating Scale (WSRS) score. Both folds must have the same NLF score at entry.

7.1 Selection of Study Population

Assessment for eligibility criteria is based on the subject's medical records, an interview with the candidate subject and investigator judgment. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be considered for participation.

7.2 Inclusion Criteria

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

1. Is 22 - 65 years of age.
2. Has symmetrical NLFs of moderate or severe intensity (grade 3 or 4) on WSRS grade as determined by the independent blinded evaluator and confirmed by the treating investigator at baseline.
3. Both folds must have the same NLF score at baseline.
4. Has signed an informed consent.
5. Understands and accepts the obligation not to receive any other facial procedures below the eyes during the study.
6. Understands and accepts the obligation to present for all scheduled follow-up visits and is logistically able to meet all study requirements.
7. Subjects of childbearing potential must have a negative pregnancy test result and must not be lactating at the Screening/Baseline Visit and be willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study. Women will be considered if one of the following conditions is documented on the medical history:
    a. Postmenopausal with last menstrual bleeding at least 12 months prior to study; and
    b. Without a uterus and/or both ovaries.

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. Has received surgical permanent implants, grafting, or surgery below the eyes on the face prior to injection or lower lid blepharoplasty within 6 months prior to injection.
2. Has received within the specified (washout) period or plans to receive treatment during the study conduct with a non-permanent facial filler in any facial area below the eyes:
   a) 12 months prior to study start - hyaluronic acid [HA] or collagen
   b) 18 months prior to study start - calcium hydroxylapatite [CaHA]
3. Has received at any time or plans to receive during the study a permanent facial filler (e.g. poly L-lactic acid [PLLA], polymethyl-methacrylate [PMMA], silicone) below the eyes.
4. Has received within the past 6 months or plans to receive during the study facial dermal resurfacing procedures (e.g. chemical peel, dermabrasion, ablative laser resurfacing), non-invasive skin-tightening (e.g. Thermage), botulinum toxin injections, mesotherapy, or fat injections below the eyes.
5. Has received in the past 2 weeks or plans to receive during the study any prescription wrinkle therapies (e.g. RENOVAÒ), topical steroids, skin irritating topical preparations, or pigmenting agents (self-tanning agents) for use on the face.
6. Has received in the past 2 months, or plans to receive immunosuppressive medications or systemic steroids (intranasal/inhaled steroids acceptable) during the study.
7. Has an acute inflammatory process or infection, active herpes infection, or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of adverse events (AEs).
8. Has a known bleeding disorder or has received or is planning to receive anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin), anti-inflammatory drugs (oral/injectable corticosteroids or NSAIDs (e.g., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, e.g., Vitamin E, garlic, gingko), from 10 days before injection to 3 days after injection.
9. Has a history of known liver or renal function disease/disorder or has clinically significant laboratory values at baseline.
10. Has a known history of allergic/anaphylactic reactions, including hypersensitivity to lidocaine or anesthetics of the amide type, or any of the device components.

11. Has a history of hyper- or hypo-pigmentation in the NLFs, keloid formation, or hypertrophic scarring.
12. Has recently lost or has the intention to lose a significant amount of weight ≥ 2 Body Mass Index (BMI) units] during the course of the study.
13. Has any other medical condition with the potential to interfere with the study's conduct or assessments, or increase the risk of AEs.
14. Has participated in a study in the last 30 days or is enrolled or plans to enroll in any other interfering investigational study during participation in the study.
15. Is an employee or direct relative of an employee of the investigational department in site or the sponsor.

7.4 Removal of Subjects from Treatment or Assessment

7.4.1 Discontinuation of Subjects

A 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 will 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.
- Any AE for which the subject would be unable to continue in the study.
- Any subject who becomes pregnant may complete the study and will be followed for safety assessments.

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 any subject lost to follow-up, and all such efforts should be documented in the subject file. If appropriate, according to local regulations, Ethic Committee(s) (EC) and Competent Authorities should be informed.

7.4.2 Premature Termination or Suspension of the Study or a Study site

The study or a study site can be prematurely terminated or suspended by the sponsor. 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 EC has decided 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 EC, and regulatory authorities of the termination or suspension of the study, as appropriate.

8 TREATMENTS

8.1 Investigational Product(s)

In this trial investigational products (IPs) are study product (Radiesse) and control product (Restylane).

Radiesse (1.5mL) syringe in bulk along with 27G Needle and Restylane (0.5 mL/1 mL) with a thin gauge needle (30 G x ½") will be provided to the site. Radiesse will be as investigational product for this clinical use only.

8.1.1 Radiesse

See in the **Appendix 1**: Instructions for Use of Radiesse®

8.1.1.1 *Description of Investigational Product(s)*

Radiesse Injectable Implant, Merz North America, Inc.

Radiesse injectable implant is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant. The principle component is synthetic CaHA suspended in a gel carrier that consists primarily of water (sterile water for injection, United States pharmacopeia (USP)), glycerin (USP), and sodium carboxymethylcellulose (USP). Radiesse injectable implant (1.5mL syringe unit) has a CaHA particle size range of 25-45 microns and should be injected sub-dermally with a 27 gauge needle. Additional information regarding the product and administration technique will be provided in Section 8.1.1.5 of the clinical study protocol and the proposed China IFU.

8.1.1.2 *Features of the Device*

Radiesse injectable implant (dermal filler) consists of CaHA microspheres suspended in a carboxymethylcellulose gel carrier. The radiopaque CaHA microspheres are uniform in size and shape and function as a scaffold for natural collagen growth as the gel carrier is slowly replaced by the body's own connective tissue. Calcium hydroxylapatite is the primary component of bone and teeth. In particle form, it has been used for many years as inlay grafts for bone regeneration in dentistry, for the correction of oral and maxillofacial defects, as orbital implants, and coating for orthopedic prostheses[1].

8.1.1.3 *Mechanism of Action*

Radiesse provides immediate volumization to the injected area of the skin. Additionally, it stimulates the skin's own regeneration abilities, as new collagen is produced over the following weeks and months.

8.1.1.4 *Indications, Contraindications and Warnings*

Indications

Radiesse injectable implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds and it is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

Radiesse injectable implant is also indicated for hand augmentation to correct volume loss in the dorsum of the hands.

Contraindications

- Contraindicated for subjects with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Not to be used in subjects with known hypersensitivity to any of the components.
- Radiesse injectable implant is contraindicated for subjects with bleeding disorders.

Warnings

- Introduction of RADIESSE® into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting, soft tissue fillers, for example inject RADIESSE® slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Use of RADIESSE® injectable implant in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
- Injection procedure reactions have been observed consisting mainly of short-term (i.e., < 7 days) bruising, redness and swelling. Refer to adverse events sections for details.

- Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of RADIESSE® injectable implant occurs.

- The safety and effectiveness for use in the lips has not been established. There have been published reports of nodules associated with the use of RADIESSE® injectable implant injected into the lips.

Precautions

- In order to minimize the risks of potential complications, RADIESSE® should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.

- In order to minimize the risks of potential complications, Healthcare practitioners should fully familiarize themselves with the product, the product educational materials and the entire package insert.

- The calcium hydroxylapatite (CaHA) particles of RADIESSE® injectable implant are radiopaque and are clearly visible on CT Scans and may be visible in standard, plain radiography. Patients need to be informed of the radiopaque nature of RADIESSE® injectable implant, so that they can inform their primary care health professionals as well as radiologists. In a radiographic study of 58 patients, there was no indication of RADIESSE® injectable implant potentially masking abnormal tissues or being interpreted as tumors in CT Scans.

- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that the patients are aware of signs and symptoms of potential complications.

- As with all transcutaneous procedures, RADIESSE® injectable implant injection carries a risk of infection. Infection may necessitate attempted surgical removal of RADIESSE®. Standard precautions associated with injectable materials should be followed.

- Patients who are using medications that can prolong bleeding, such as aspirin or warfarin, may, as with any injection, experience increased bruising or bleeding at the injection site.

- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with RADIESSE®

injectable implant, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RADIESSE® injectable implant is administered before the skin has healed completely after such a procedure.

- Safety of RADIESSE® injectable implant beyond 3 years has not been investigated in clinical trials.

- Safety of RADIESSE® injectable implant for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.

- The safety of RADIESSE® injectable implant in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied.

- The safety of RADIESSE® injectable implant with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.

- Injection of RADIESSE® injectable implant into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

- No studies of interactions of RADIESSE® injectable implant with drugs or other substances or implants have been conducted.

- Safety and effectiveness in the periorbital area has not been established.

- The patient should be informed that he or she should minimize exposure of the treated area to extensive sun or heat exposure for approximately 24 hours after treatment or until any initial swelling and redness has resolved.

- Universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.

- RADIESSE® injectable implant is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged. Do not use if the syringe end cap or syringe plunger is not in place.

- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.

- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.

- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.

8.1.1.5 *Dosage and Administration*

[redacted] only 1.5 cc/syringe of Radiesse will be used in this study. Radiesse is provided as sterile, single use, non-pyrogenic devices. Each unit contains a 1.5 mL/syringe of injection media in a pre-filled syringe.

Injection: Subdermal injection.

8.1.1.6 *Technique*

The investigator determines the appropriate volume of Radiesse filler needed to obtain optimal correction at the initial and touch-up treatments.

1. Prepare subject for percutaneous injection using standard methods. The treatment injection site should be marked and prepared with a suitable antiseptic. Topical anesthesia at the injection site may be used at the discretion of the physician. If topical anesthesia is used, is must be recorded on the CRF.

2. Prepare the syringes of Radiesse injectable implant and the injection needle (s) before the percutaneous injection. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe.

3. Remove foil pouch from the carton. 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.

4. Peel or twist apart the needle packaging to expose the hub.

5. Remove the Luer-syringe cap from the distal end of the syringe prior to attaching the needle. The syringe of Radiesse injectable implant can then be twisted onto the Luer-lock fitting of the needle taking care not to contaminate the needle. Discard needle package. The needle must be tightened securely to the syringe and primed with Radiesse injectable implant. If excess implant is on the surface of the Luer-lock fittings, it will need to be wiped clean with sterile gauze. Slowly push the syringe plunger until Radiesse injectable implant

extrudes from the end of the needle. If leakage is noted at the Luer fitting, it may be necessary to tighten the needle, or to remove the needle and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle.

6. Locate the initial site for the implant. Scar tissue and cartilage may be difficult or impossible to treat. Avoid if possible, passing through these tissue types when advancing the injection needle.

7. The amount injected will vary depending on the site and extent of the restoration or augmentation desired. Radiesse injectable implant should be injected sub-dermally.

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

9. Insert needle with bevel down at approximately a 30° angle to the skin. Needle should slide under the dermis to the point you wish to begin the injection.

10. 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. One needle jam occurred in the nasolabial fold clinical study. Needle jams are more likely with use of needles smaller than 27gauge I.D.

11. Advance the needle into the sub-dermis to the starting location. Carefully push the plunger of the Radiesse injectable implant syringe to start the injection and slowly inject the implant material in linear threads while withdrawing the needle. Continue placing additional lines of material until the desired level of correction is achieved.

12. Apply slow continuous even pressure to the syringe plunger to inject the implant as you withdraw the needle. The implant material should be completely surrounded by soft tissue without leaving globular deposits. The injected area may be massaged as needed to achieve even distribution of the implant.

13. Use once and discard in accordance with local safety standards.

If subject needs additional treatments during this study, for example emergency rescue, anesthesia, pain management pill as well as the proper device and so on, treating investigator could provide them by themselves.

8.1.1.7 *Storage*

Radiesse injectable implant should be stored at a controlled room temperature between 15℃ and 32℃ (59℉ and 90℉). The expiration date, when stored in these temperatures, is three years from date of manufacture for the 1.5mL syringe volume. Do not use if the expiration date has been exceeded.

8.1.1.8 *Duration of Treatment*

Subjects will have an initial injection and an option of a touch-up injection in one or both NLFs at Week 4 after the initial injection with the treatment to which they were randomized.

8.1.2 Restylane (study control/comparator)

See in the **Appendix 2**: Instructions for Use of Restylane ®.

8.1.2.1 *Description of Investigational Product(s)*

Restylane (Q-Med AB) will also be supplied by Merz.

Restylane is a clear, colorless gel without particulates. Restylane contains a gel of modified hyaluronic acid of nonanimal origin. Hyaluronic acid is a natural macromolecular substance which occurs as an important structural element in the skin and in subcutaneous and connective tissues as well as in the synovial tissue and fluid. Hyaluronic acid is metabolized and degraded normally in the body. All raw materials used in the manufacturing process are of non-animal origin. Restylane is administered using a thin gauge needle (30 G x ½") into the mid dermis. Additional information regarding the product and administration technique will be provided in referenced to the current IFU. Refer to Appendix 2.

8.1.2.2 *Features of the Device*

The Restylane dermal filler gel resembles the body's own hyaluronic acid, and is specifically designed to work within the different layers of the skin to replace or restore facial volume and improve the quality and integrity of the skin.

8.1.2.3 *Mechanism of Action*

Restylane is a dermal tissue filler used to restore the skin contours to the desired level of correction through augmentation of facial skin. Restylane will degrade gradually in the body, typically 6-12 months after injection. With degradation the filler effect will disappear. The patients, who want to keep the filler effect, can receive follow-up injection when the filler effect disappears. The filler effect remains for longer than 6 months in the majority of patients as shown in the Chinese study, where the patients were injected in the nasolabial folds.

8.1.2.4 *Indications, Contraindications and Warnings*

Indications

Restylane is intended to be used for facial tissue augmentation by injections into the mid dermis to correct moderate to severe nasolabial folds.

Contraindications

- Restylane is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- Restylane should not be used in the following situations:
  - Permanent implant in the same area.
  - Non-permanent implant placed in the same area during the previous 6-12 months.
  - If no information is available on the type of implant.
- Do not use in patients with bleeding disorders or patients who are taking thrombolytics or anticoagulants, or have taken inhibitors or platelet aggregation in the preceding 2 weeks.
- Restylane should not be used in or near anatomic sites where there is active skin disease, inflammation, infection or related conditions.

Warnings

- Restylane is only intended for use as an intradermal implant. Do not resterilize Restylane.
- Do not inject intravascularly. Injection into blood vessels may rarely lead to transient ischemia or even necrosis affecting the tissue supplied by the blood vessel.
- Restylane should not be mixed with other products before implantation of the device.
- The product is for single use only.
- Do not use if package is damaged.

8.1.2.5 *Dosage and Administration*

Restylane is supplied in a disposable glass syringe (0.5 mL/syringe, or 1 mL/syringe) with a luer-lock fitting. Restylane is co-packed with sterilized needle(s) as indicated on the carton, 30 G x ½".

Injection site: Restylane should be injected into the middle part of the dermis layer of the facial skin.

8.1.2.6 *Technique*

The dosing and administration of Restylane should follow the Restylane China IFU.

- The doctor has to inform the patients about the indications, expected result and duration of filler effect, contraindications, precautions, warnings and potential adverse events before treatment.
- Restylane is administered using a thin gauge needle (30 G x ½") by injecting the material into the dermis. Before injecting, press the syringe plunger carefully until a small droplet is visible at the tip of the needle.
- During the injection it is recommended that the eye of the needle should face upwards. Inject Restylane while pulling the needle is pulled out from the skin to prevent material from leaking out from the injection site.
- Additional implantations of Restylane may be necessary to achieve the desired level of correction if patients are not satisfied with the filler effect.

8.1.2.7 *Storage*

Store up to 25℃ (77℉). Protect from freezing and sunlight. This shelf life of the product is 36 months from the data of manufacture.

8.1.2.8 *Duration of treatment*

Subjects will have an initial injection and an optional touch-up injection in one or both NLFs 4 weeks after the initial injection.

8.2 Disposition of Investigational Product(s)

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the protocol. The sponsor or designee shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include

a. The date of receipt,

b. Identification of each investigational device (batch number/serial number or unique code), :

c. The expiry date, if applicable,

d. The date or dates of use,

e. Subject identification,

f. Date on which the investigational device was returned/explanted from subject, if applicable, and

g. The date of return of unused, expired or malfunctioning investigational devices, if applicable.

The Investigator will maintain adequate records of the receipt and disposition of the investigational device. An Inventory/Device Accountability Log will be used. All unused investigational devices must be returned to the Sponsor when enrollment is complete or as otherwise deemed necessary (e.g., expired devices).

No investigational devices should be discarded, unaccounted for, or destroyed.

8.3 Treatment Administration

8.3.1 Randomization Procedures

Treatment per NLF will be assigned via an Interactive Web Response System (IWRS). The randomization schedule will be provided by an independent biostatistician at the Contract Research Organization (CRO).

8.3.2 Treatment Compliance

All device administration (injection) will be performed on site by the treating investigator. The subjects will not be dispensed any investigational material.

8.3.3 Treatment Method

Subject's NLFs will be treated with an initial injection of Radiesse on one side of the face and Restylane on the other side of the face with an optional touch-up injection at 4 weeks after initial treatment in order to achieve optimal correction. Restrictions during the study:

The following concomitant therapies will be prohibited during the study:

- No application of any new over-the-counter or prescription, oral or topical, anti-wrinkle products near the NLF region during participation in this study. (Use of sunscreens and continued therapy with some cosmeceuticals, i.e., alpha hydroxyl acids, glycolic acids, retinol, or retinoic acids, is allowed if the regimen was established > 90 days prior to enrollment).
- No cosmetic facial plastic surgery or oral surgery procedures during participation in the study (i.e., orthodontia, extraction, implants).

- No dermal therapies (i.e., dermal fillers, toxin treatments, facial ablative or fractional laser, microderm abrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage] and surgical procedures) in the lower face and jaw line region during participation in the study.
- No systemic immunosuppressive medications or topical immunomodulatory preparations in the mid and lower face (e.g. topical steroids, calcineurin-inhibitors or imiquimod). Intranasal / inhaled steroids are allowed.
- No anti-coagulation, anti-platelet, or thrombolytic medications (i.e., warfarin), anti-inflammatory drugs (i.e., aspirin, ibuprofen), or other substances known to increase coagulation time (vitamins or herbal supplements, i.e., vitamin E, garlic, gingko) to 3 days post injection.

The following actions and treatments are prohibited as stated as long as any initial skin reddening/swelling has also subsided:

- Applying makeup and touching/pressing of the treated parts of the face up to 12 hours after treatment.
- Use of skin-irritating agents (keratolytic, antiseborrheic, anti-acne agents) on the face for at least 7 days after treatment.
- Use of pigmenting agents (self-tanning agents, depigmenting agents) on the face for at least 7 days after treatment.
- Exposure to extreme cold or heat (sauna, Turkish bath) for at least 14 days after treatment.
- Prolonged exposure to natural or artificial sources of UV radiation (e.g., sunlight or tanning booth) for at least 14 days after treatment.

8.4 Blinding Procedures

All subjects will be treated with both Radiesse and Restylane in a split-face design. Each NLF (designated right/left) will be assigned at random via an IWRS. The treating investigator will be un-blinded to the treatment per fold. Both the subject and the blinded evaluator (must be a qualified physician) will be blinded to the randomized treatment for each NLF throughout the duration of the study.

If the subject requires a touch-up of the NLF(s) at Week 4, the same randomized product must be administered to the respective NLF(s) while maintaining the blind mentioned above.

To ensure that the blind is maintained, subjects will have their upper face masked or covered during initial and optional touch-up treatments. Subjects will be instructed not to discuss treatment and or the ratings with the blinded evaluator. Injecting investigator will not be allowed to discuss randomization assignments with the subject or the blinded evaluator(s).

It is important that the blinded evaluator(s) do not have access to any study documents that would break the blind.

8.4.1 Emergency envelopes

No emergency envelopes will be prepared as the treating investigator remains unblinded.

8.4.2 Unblinding procedures

The blind for all personnel involved in this clinical investigation will not be broken until the Blind Data Review Meeting (BDRM) has convened, the Statistical Analysis Plan (SAP) has been finalized, and the database has been locked. The statistical analysis will proceed after the unblinding, which will be documented.

9 STUDY ASSESSMENTS

9.1 Clinical Evaluations

9.1.1 Effectiveness Assessments

9.1.1.1 *Wrinkle Severity Rating Scale (WSRS)*

The WSRS scale will be used to measure clinical effectiveness of the study products by a trained, blinded evaluator performing the assessments. If a NLF treatment is scheduled during a study visit, the NLF assessment must be completed prior to treatment. Ratings are done at each visit. The WSRS scale is as follows:

Table 1 The Wrinkle Severity Rating Scale (WSRS)

Score	Description
1	**Absent**: Absent: No visible fold; continuous skin line
2	**Mild**: Shallow but visible fold with a slight indentation; minor facial feature; implant is expected to produce a slight improvement in appearance
3	**Moderate**: Moderately deep folds; clear facial feature visible at normal appearance but not when stretched; excellent correction is expected from injectable implant
4	**Severe**: Very long and deep folds; prominent facial feature; less than 2-mm visible fold when stretched; significant improvement is expected from injectable implant
5	**Extreme**: Extremely deep and long folds, detrimental to facial appearance; 2- to 4-mm visible V-shaped fold when stretched; unlikely to have satisfactory correction with injectable implant alone

Figure 2 WSRS scale

Absent	Mild	Moderate	Severe	Extreme
1	2	3	4	5

Prior to study initiation, at least one blinded evaluator at each site will be trained and qualified by the study sponsor to perform the rating using the WSRS scale.

9.1.1.2 *Blinded Evaluator Global Aesthetic Improvement Scale (GAIS):*

The blinded evaluator will rate each NLF for the global aesthetic improvement using the baseline pre-treatment photos for comparison. The evaluator will rate the current cosmetic result for each NLF according to the GAIS based on live assessments during the visit compared with photographs taken at baseline before administration of treatment on each NLF. The following categorical scale will be used:

Table 2 Global Aesthetic Improvement Scale

Score	Rating	Description
+3	Very much improved	Optimal cosmetic result for the implant in this subject
+2	Much improved	Marked improvement in appearance from the initial condition, but not completely optimal for this subject
+1	Improved	Obvious improvement in appearance from the initial condition
0	No change	The appearance is essentially the same as baseline
-1	Worse	The appearance is worse than the original condition
-2	Much worse	Marked worsening in appearance from the initial condition
-3	Very much worse	Obvious worsening in appearance from initial condition

[redacted]

[redacted]

[redacted]

9.1.1.4 *Photography of NLFs*

Sites will receive a photography manual that describes how photographs will be standardized and managed. Photographs will be taken at Visit 2 (Baseline prior to treatment), Vist 4 and Vist 5.

9.1.2 Safety Assessments

9.1.2.1 *Adverse Events*

All adverse events (AEs) reported by study subjects, investigators, or other study staff through this study will be recorded.

If a serious AE or unanticipated serious device-related effect occurs, study subjects should return to the site for an unscheduled visit. Additionally, AEs will be assessed at every visit.

9.1.2.2 *Injection Site Reaction Subject Diaries*

Following initial treatment and optional touch-up injection(s), a 30 day take-home patient diary will be dispensed. The subject will record daily any site injection reactions. Take-home diaries will be returned to the site at next visit.

Investigators will review the Injection Site Reaction Diaries and determine if any of the reactions should be recorded in the eCRF as AEs.

9.1.2.3 *Clinical laboratory Tests and Serum Pregnancy Tests*

Non-fasting clinical laboratory tests will be performed at Visit 1 (Screening), Visit 5 (Month 6), and Visit 7 (End of Study). These labs include hematology, urine test and biochemistry to rule out any underlying disease that may exclude the subject from participation.

Serum pregnancy test will be performed on all women of childbearing potential at Visit 2 (Baseline), Visit 5 (Month 6) and at Visit 7 (End of Study).

Visit 1 (Screening) and Visit 2 (Baseline) maybe conducted on the same day if laboratory results are available and assessed by the investigator prior to treatment. If the serum pregnancy test results cannot be provided on the same day on Visit 2 (prior to injection) then the serum pregnancy test may be performed within 3 days before baseline visit so that a negative result is available prior to injection. Serum pregnancy results must be available prior to injection.

9.1.2.4 *Vital Signs*

Vital signs will be measured on subjects after they have been seated for about 5 minutes. Resting heart rate, blood pressure (systolic and diastolic, preferably on the same arm each time) and respiration rate will be measured at Visits 1, 2, 3, 5 and 7.

9.1.3 Other Assessments

[redacted]

9.1.3.2 *Demographics, Weight and Height*

Demographic information will be collected at Screening for all subjects and recorded in the eCRF. Demographic information includes age gender, race, weight, height and Fitzpatrick skin type. This will be collected according to local rules and regulations. Weight will also be collected at Visits 2, 5, and 7.

9.1.3.3 *Medical History, prior/concomitant medication and non-drug therapy*

Medical history, prior/concomitant medication and non-drug therapy relevant to inclusion/ exclusion criteria and restrictions will be collected as part of the screening assessment regardless of onset time. Findings will be recorded in the eCRF.

9.2 Visit Schedule

9.2.1 Study Time Points

The planned study period is 12 Months consisting of the following visits:

- Visit 1 (Screening): Screening and Baseline Visits may be the same day (if laboratory results are available prior to treatment)
- Visit 2 (Baseline/Treatment): Day 1, Injection
- Visit 3 (Week 4 / Month 1 Post Treatment): Optional touch-up with the same randomized product
- Visit 4 (Month 3 Post Treatment)
- Visit 5 (Month 6 Post Treatment): Primary endpoint
- Visit 6 (Month 9 Post Treatment)
- Visit 7 (Month 12 Post Treatment)

9.2.2 Data Collected

Visit 1 (Screening, Day -14 to Day 0)

The following data will be collected:

- Obtain informed consent
- Evaluate inclusion/exclusion criteria
- Subject demographics
- Vital signs: heart rate, blood pressure, and respiration rate
- Height
- Weight
- Laboratory Assessments: hematology, urine test and biochemistry
- WSRS scale assessment
- Medical history

- Concomitant Medications/Treatments
- Collect adverse events (AEs) and assess AEs

Visit 2 (Baseline/Initial Treatment, Day 1)

Screening and baseline visits may occur on the same day if laboratory test results are available prior to treatment.

The following data will be collected:

- Evaluate inclusion/exclusion criteria
- Weight
- Vital signs: heart rate, blood pressure and respiration rate
- Serum Pregnancy test for women of childbearing potential only
- Concomitant Medications/Treatments
- WSRS scale assessment
- Photograph(s) (pre-treatment)
- Randomization assignment for each NLF
- Dermal filler injections
- [redacted]
- Injection Site Reaction diary dispensed
- Collect AEs and assess AEs

Visit 3 (Week 4 / Month 1, Post Treatment; optional touchup, Day 28+ 7days)

Subjects may receive an optional touch-up injection at the 4-week post-treatment visit in order to achieve optimal correction. If touch-up is required on one or both NLFs, investigators must use the same NLF filler product as received during the initial treatment per the randomization schedule and must maintain the blind.

The following data will be collected:

- Vital signs: heart rate, blood pressure, and respiration rate
- [redacted]

- [redacted]
- [redacted]
- Collect Injection Site Reaction diary and assess for AEs
- Concomitant Medications/Treatments
- If touch-up is required on one or both NLFs
  - Obtain original randomization assignment for each NLF
  - Dermal filler injections
  - [redacted]
  - Site Reaction diary dispensed
- Collect AEs and assess AEs

Visit 4 (Month 3 ± 7 days)

The following data will be collected:

- Collect Injection Site Reaction diary (if touch-up done at Visit 3) and assess for AEs
- Collect AEs and assess AEs
- Concomitant Medications/Treatments
- Photograph(s)
- [redacted]
- [redacted]
- [redacted]

Visit 5 (Month 6 ± 7 days)

The following data will be collected:

- Vital signs: heart rate, blood pressure, and respiration rate
- Laboratory Assessments: hematology, urine test and biochemistry
- Weight

- WSRS scale assessment
- Photograph(s)
- Blinded evaluator GAIS
- [redacted]
- Serum pregnancy test, for females of childbearing potential
- Collect AEs and assess AEs
- Concomitant Medications/Treatments

Visit 6 (Month 9 ± 7 days)

The following data will be collected:

- [redacted]
- [redacted]
- [redacted]
- Collect AEs and assess AEs
- Concomitant Medications/Treatments

Visit 7 (Month 12 ± 7 days)

The following data will be collected:

- Vital signs: heart rate, blood pressure, and respiration rate
- Weight
- Laboratory assessments: hematology, urine test and biochemistry
- Serum Pregnancy test for women of childbearing potential only
- [redacted]
- [redacted]
- [redacted]
- Collect AEs and assess AEs

- Concomitant Medications/Treatments

9.2.3 Overview of Study Activity/Visit Schedule

Table 4 Visit Schedule

Assessment	Visit schedule						
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Timepoint	**Day 0[1] (Day -14 to Day 0)**	**Day 1[1]**	**Week 4 /Month 1 (Day 28 + 7 d)**	**Month 3 ± 7 d**	**Month 6 ± 7 d**	**Month 9 ± 7 d**	**Month 12 ± 7 d**
	Screening	**Baseline/ Initial Treatment**	**Touch-up[2] (optional)**				
			Effectiveness & Safety Follow-up				
Inclusion/Exclusion	X	X					
Informed consent	X						
Subject demographics	X						
Vital signs[3]	X	X	X		X		X
Height	X						
Weight	X	X			X		X
Laboratory assessment[4]	X				X		X
Obtain randomization		X					
Dermal filler injection		X	X[5]				
WSRS scale assessment	[redacted]				X	[redacted]	
Photographs		X		X	X		
Blinded Evaluator GAIS	[redacted]				X	[redacted]	
[redacted]							
Injection Site Reaction diary dispensed		X	X[7]				

Assessment	Visit schedule						
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Timepoint	**Day 0[1] (Day -14 to Day 0)**	**Day 1[1]**	**Week 4 /Month 1 (Day 28 + 7 d)**	**Month 3 ± 7 d**	**Month 6 ± 7 d**	**Month 9 ± 7 d**	**Month 12 ± 7 d**
	Screening	**Baseline/ Initial Treatment**	**Touch-up[2] (optional)**				
			Effectiveness & Safety Follow-up				
Collect Injection Site Reaction diary			X	X[7]			
Collect AEs and assess AEs	X	X	X	X	X	X	X
Serum Pregnancy test[8]		X[9]			X		X
Medical history	X						
Concomitant Medications/Treatments	X	X	X	X	X	X	X

[1] Screening (Day 0) and baseline (Day 1) may occur on the same day (if laboratory results are available prior to treatment).

[2] Subjects may receive an optional touch-up in order to achieve optimal correction at Week 4.

[3] Vital signs: heart rate, blood pressure, and respiration rate.

[4] Laboratory Assessments include hematology, urine test and biochemistry.

[5] If touch-up is required, the treatment investigators must use the same product on the NLF as that of the initial treatment per the randomization schedule.

[redacted]

[7] If touch-up is required, Injection Site Reaction diary should be dispensed at Week 4 and collected at Month 3.

[8] Only for female subjects of childbearing potential (e.g. not post-menopausal for at least one year or has not had a hysterectomy or tubal ligation).

[9] If the serum pregnancy test results cannot be provided on the same day on Visit 2 (prior to injection) then the serum pregnancy test may be performed within 3 days before baseline visit so that a negative result is available prior to injection.

10 SAFETY ASSESSMENTS

10.1 AEs

The general definition for an adverse event (AE) is an untoward medical occurrence which does not necessarily have a causal relationship to the study product. An AE can therefore be any unfavorable, unintended, or untoward clinical sign (including an abnormal laboratory finding), unintended disease or injury, a symptom or disease temporally associated with the use of the study product, whether or not considered related to that device. An AE may also apply to other users or persons as noted in Note 3 below.

NOTE 1: This includes events related to the study product(s).

NOTE 2: This includes events related to the procedures involved (any procedure in the clinical study protocol).

NOTE 3: For users or other persons this is restricted to events related to the study product(s).

AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the subject, uncovered by review of concomitant medications or therapies, and/or observed by the investigation site staff. The investigator will determine the description (sign, symptom, or diagnosis), onset, resolution, seriousness, severity, cause and action taken for any event.

Disease signs and symptoms that existed prior to ICF sign off are not considered AEs. Recurring symptoms associated with pre-existing conditions are not considered AEs unless they have a clinically significant increase in severity and/or frequency.

Elective treatments planned before screening and which are documented in the subject's source data are usually not regarded as AEs. However, elected procedures should be postponed, if possible, until the subject completes their participation in the investigation. All adverse events will be collected on each subject until to the 12-month follow-up visit. The subject's course must be monitored until the event has subsided or, in a case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

10.1.1 Definition of Intensity

The investigator is required to grade the severity /intensity of each AE. 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 electronic Case Report Form (eCRF) AE report form). In such situations, the investigator should make a judgment based on personal experience.

10.1.2 Definition of Causal Relationship

An AE is considered to be "related" to IP(s) if a causal relationship between the IP(s) and an AE is at least a reasonable possibility (i.e., the relationship cannot be ruled out). In this case, the event is considered an ADE. If the event is serious (see below), it is a serious adverse device effect (SADE).

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

10.1.3 Categories of Outcome

The reportable outcomes and/or sequelae of an AE are as follows:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered/resolved with sequelae.
- Fatal.
- Unknown.

If there is more than one AE, only the AE leading to death will be attributed with a "fatal" outcome.

10.2 Adverse Device Effect (ADE)

An ADE is defined as an AE related to the use of a study product.

NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the IFU, the deployment, the implantation, the installation, the operation, or any malfunction of the study product(s).

NOTE 2: This definition also includes any AE that is a result of a use error or intentional misuse.

10.3 Device Deficiency

A device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Note: A device deficiency that may cause SAE and have led to an SADE (for definition see Section 10.5) is to be reported in the same way as an SAE.

10.4 Serious Adverse Event

The definition for a serious adverse event (SAE) is the adverse event (AE) that:

1. Led to death;
2. Led to serious deterioration in the health of the subject, that either resulted in:
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the Clinical Investigation Protocol, without serious deterioration in health is not considered a serious adverse event.

If a subject experiences an additional AE that prolongs a pre-planned hospitalization this is considered to be an SAE and should also be reported as an SAE. Pre-planned admissions must be recorded in the subject's source documentation.

For the investigator: Once awareness for that SAE occurs, investigator should take appropriate treatment measures for subjects immediately and must fill in the SAE-Form and report to the medical device clinical trial institution within 24 hours.

For Medical Device Clinical Trial Institution: The institution will further report SAE to corresponding EC, located Food and Drug Administration department and provincial health authority, and sponsor as soon as possible no later than 24 hours. For death, the institution and investigator should provide all the necessary information to EC and sponsor.

For the sponsor: Serious adverse events must be reported no later than 5 working days from the sponsor (CRO authorized by Merz) to filed Provincial Food and Drug

Administration (PFDA) and provincial health authority, and should be informed to the other investigative sites and the investigators. All SAEs that occur during the study period must be reported by telefax, telephone or e-mail of knowledge of the event.

10.5 Serious Adverse Device Effect (SADE)

Any ADE that has resulted in any of the consequences typical of an SAE, or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

10.5.1 Anticipated Serious Adverse Device Effect (ASADE)

ASADEs are those listed in the current IFU and in the IB of Radiesse and in the current IFU of Restylane®.

10.5.2 Unanticipated Serious Adverse Device Effect (USADE)

An USADE is an effect that by its nature, incidence, severity or outcome has not been identified in the current IFU, in the IB of Radiesse, and in the current IFU of Restylane®.

An USADE is defined as any device-related AE that meets any of the following:

a) is not identified in nature, severity or frequency in current literature or in the current version of the product risk analysis report;

b) is life threatening, even if temporary in nature;

c) results in permanent impairment of a body function or permanent damage to a body structure;

d) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure;

e) any device malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

10.6 Reporting Period

The period of observation for an AE extends after signing ICF with the study products until the end of the investigation (approximately 12 months after the treatment with the study products). Any medical occurrence that happens after signing ICF with the study products is an AE and has to be documented in the subject's file and in the eCRF AE report form. New AEs reported to the investigator during the observational period after the treatment with the study products must be documented, treated, and followed-up like all other AEs.

AEs will not be followed-up after the final investigation visit/safety visit, which is scheduled 12 months after the treatment with the study products. After the last batch of

queries with all collected data have been fully processed, eCRFs and the database will no longer be updated. Only SAEs and medically relevant ongoing/unknown outcome AEs will be followed-up until resolution or stabilization under the responsibility of the sponsor.

10.6.1 Handling and reporting of adverse event (AE) and device deficiency

Subjects will be carefully monitored during the clinical investigation for possible AEs.

All AEs or reactions must be reported in subject's medical records (source documents) and in the eCRF.
In addition, the investigator and staff shall also carefully report any device deficiencies. Any AEs and device deficiencies observed will be fully investigated, documented and followed up until the event is either resolved or adequately explained.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome. In this case, the primary cause of death (the event leading to death) should be recorded and reported as an SAE. "Death" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might be reported as an SAE.

Pre-existing conditions that do not worsen during the course of the clinical investigation are not reportable as AEs. To determine whether a condition has worsened, it is compared to the condition of the subject at screening.

Data pertaining to AEs will be collected during each investigation visit based on the subject's spontaneous description, through investigator inquiry, or discovered in the course of examinations done during the visit. The investigator will assess and record any AE in detail in the subject file and on the eCRF AE report form. The following information must be recorded:

- AE diagnosis or main symptom.
- Location of AE: systemic or restricted to injection area. In case of local reaction, the corresponding area should be reported.
- Date of onset.
- Time of onset (if known).
- Date of worsening.
- Time of worsening (if known).
- Severity (maximum observed; see Section 10.1.1).

- Causal relationship (see Section 10.1.2).
- Serious (yes or no).
- Outcome (see Section 10.1.3).
- Action taken with study product(s).
- AE leading to discontinuation of the investigation (yes or no).
- Stop date (and time if known).

After completion of all scheduled visit assessments, the investigator must document any AEs arising from these assessments.

For device deficiencies, the investigator will attempt to evaluate whether the deficiency might have led to an AE, if the suitable action have not been taken, intervention have not been made, or circumstances have been less fortunate.

In case of an SAE, the investigator must also complete an SAE report form and report it to the sponsor immediately, as described in Section 10.4.

In case of death, the investigator shall make every effort to obtain a copy of the autopsy report and or death certificate and transmit this, after anonymization, to the sponsor.

At visit 2 a take-home patient 30 day diary will be dispensed and after each visit the subject will record self-reported daily AEs. Take-home diaries will be returned to the site upon completion. If a serious AE or unanticipated serious device-related effect occurs, study subjects should return to the site for an unscheduled visit. Additionally, AEs will be assessed at other visits.

10.6.2 Handling and reporting of serious adverse events

All SAEs that occur during the investigation period, whether considered to be related to the study product(s) or not, must be recorded preferably by eCRF and be reported by email or telefax or telephone within 24 hours of knowledge of the event, but all SAEs or conditions which could jeopardize all investigation subjects or deaths need to be reported immediately without any delay. The investigator will report the SAE whether considered as related or not to the clinical trial management departments of the clinical trial institution. Further reporting details will be outlined in the safety management plan. SAE report forms are implemented in the eCRF.

Although all information required for completing an SAE report form may not be available within the specified time period, an initial report should be submitted if the following minimal information is available:

- An identifiable subject (number).
- A suspect product and how the treatment relates to the SAE.
- An identifiable reporting source (investigator/investigation site identification).

- An event or outcome that can be identified as serious.

For SAEs that occur during this clinical investigation the contact is:

CRO Clinical Safety Management

[redacted]
[redacted] China. [redacted]
E-mail: [redacted]
E-fax: [redacted]
Telephone: [redacted]
Cell Phone: [redacted]

The investigator must supply further supporting information within three days of knowledge of the SAE; and a detailed SAE description is an integral part of this supporting information. Follow-up reports should be sent without delay to the sponsor as an SAE report form (marked as a "follow-up" report) and accompanied by appropriate supporting documentation (e.g., hospital reports). The SAE has to be followed-up until the SAE is resolved / recovered or a plausible explanation is available. The SAE will be followed-up only in the Corporate Product Safety database after final SAE reconciliation is completed.

SAEs occurring after the end of the observational period only need to be reported if the investigator considers the event to be related to study product(s). These reports generally will not be entered into the investigation database.

10.7 Pregnancy

Each pregnancy that starts during the investigation must be reported by the investigator to the CRO within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on a pregnancy monitoring form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the study product(s). Each pregnancy has to be reported as a non-serious AE (device exposure before or during pregnancy) as well.

10.8 Technical device complaints

Complaints are defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, or performance of a medical device (EN ISO 13485).

Technical complaint report forms are provided in the ISF.

The address for reporting technical complaints is:

CRO Clinical Safety Management

[redacted], China. [redacted]
E-mail: [redacted]
E-fax: [redacted]
Telephone: [redacted]
Cell Phone: [redacted]

For the return of samples, the vendor will be responsible for it.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

This study will be monitored regularly by a qualified monitor in accordance with applicable regulations and Standard Operation Procedures (SOPs). Monitoring procedures will include one or more visits prior to study initiation as well as periodic monitoring visits during the study on a regular basis according to a mutually agreed schedule. During these visits, the monitor will check for compliance with the study protocol and applicable regulations including but not limited to assessing integrity of the source data with the eCRF entries; proper reporting of adverse events; subject eligibility and consent; and proper handling and disposition of the investigational product.

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 ECs 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 EC 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. Further details on the statistical and analytical aspects will be presented in the SAP.

Any deviations from planned analyses, the reasons for such deviation, and all alternative or additional statistical analyses that may be performed before database close or un-blinding, respectively, will be described in amendments to the clinical study protocol or the SAP. All deviations and/or alterations will be summarized in the clinical study report.

12.1 Determination of Sample Size

The estimate of the sample size is based on the following assumptions:

- Estimate of treatment effects (i.e. proportion of responders) on Test (Radiesse) and Control (Restylane) sides are at least equal, i.e. $P_{test} >= P_{control}$ (or $D = P_{test} - P_{control} >= 0$).
- Non-inferiority margin, $\Delta = 10\%$ (i.e., maximum negligible difference between the test and control proportions).
- Type I error, $\alpha = 0.025$.
- Type II error $\beta = 0.2$ (i.e. statistical power, $1-\beta = 0.8$ or 80%).
- Proportion of pairs with discordant responses $\eta = 0.175$ (i.e. 17.5%).

Using the above assumptions for sample size calculation in nQuery yields 138 effectiveness evaluable subjects needed to carry out the non-inferiority hypothesis associated with the primary effectiveness endpoint. Accounting for a 20% attrition (attributable to dropout of subject and major protocol deviations), overall 20% more subjects will be enrolled resulting in a total of approximately 174 subjects that will be randomized into this trial.

This is a multi-center, competitive enrollment study. The target number of subjects to be enrolled per investigational site is 44. In order to ensure that adequate subjects are enrolled per investigational site for determination of treatment effect homogeneity (or lack thereof), a minimum of approximately 22 and maximum of approximately 66 subjects will be enrolled per investigational site. The specified proposed minimum and maximum number of subjects to be enrolled per investigational site minimizes the probability of any one site having a preponderance of treatment effect.

12.2 Analysis Sets

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

12.2.1 Randomized Set

The randomized set is defined as all subjects randomized into the study.

12.2.2 Safety Evaluation Set

The Safety Evaluation Set (SES) is defined as all subjects who receive an investigational product.

12.2.3 Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects randomized and who receive an investigational product with at least one post-baseline effectiveness assessment.

12.2.4 Per Protocol Set

The Per Protocol Set (PPS) is defined as the subset of the FAS without any major protocol deviations. Major protocol deviations will be finalized during the BDRM prior to database lock

12.3 Variables for Analysis

12.3.1 Effectiveness Variables

12.3.1.1 *Primary Effectiveness Variable*

The primary effectiveness variable is the treatment success at Month 6. Treatment success is defined as a ≥ 1-point improvement in NLF from baseline as assessed by a blinded evaluator on a 5-point WSRS scale.

12.3.1.2 *Secondary Effectiveness Variables*

The secondary effectiveness variable is the "improvement" in the blinded evaluator's Global Aesthetic Improvement Scale (GAIS) score for the NLF at Month 6. An "improvement" on the GAIS will be classified as "improved", "much improved", or "very much improved".

[redacted]

12.3.2 Safety Variables

Adverse events (AEs) including serious adverse events (SAEs), AEs related to treatment as assessed by the investigator, and AEs leading to discontinuation during the study. Other safety variables include vital signs and clinical laboratory assessments.

12.3.3 Other Variables

Other variables include

[redacted]

- Demographics
- Medical History
- Concomitant Medications/Treatments

12.4 Statistical Analysis Methods

12.4.1 General Considerations

All statistical analyses will be performed using SAS statistical analyses software (Version 9.2 or a newer version).

All safety analyses will use the SES. The primary effectiveness and secondary effectiveness analyses will be carried out on the PPS and for sensitivity of their analyses on the FAS. All other effectiveness (not primary and not secondary) analyses [redacted]

12.4.2 Effectiveness Endpoints

12.4.2.1 *Primary Effectiveness Endpoint*

The primary effectiveness endpoint is the difference in proportions of responding NLF sides (NLF sides with treatment success) in the Radiesse and Restylane groups at Month 6. The difference in proportions (D) is defined as the difference between the proportion of responders on the side treated with Radiesse (P_{test}) and the proportion of responders on the side treated with Restylane ($P_{control}$), i.e.:

$$D = P_{test} - P_{control}$$

As a result thereof, the null and the alternative hypothesis notations will be as follows:

$$H_0 : D \leq -\Delta \text{ (null) versus } H_1 : D > -\Delta \text{ (alternative)}$$

To test the non-inferiority of test in comparison to control, a two-sided 95% confidence interval (CI) will be constructed around D. The non-inferiority margin Δ, the clinically negligible difference, is 0.10 (or 10.0%). H_0 will be rejected if the lower bound of the 2-sided 95% CI lies above the non-inferiority margin of –Δ (–10%), i.e. a conclusion of non-inferiority of Radiesse to Restylane.. The two-sided 95% CI for the differences between proportions (paired) will be constructed using the Newcombe's recommended method[8] (Newcombe, 1998, method 10). The confirmatory analysis will be based on the PPS using observed values only.

12.4.2.2 *Secondary Effectiveness Endpoint*

The secondary effectiveness endpoint is the difference between the proportions (π_{test} - $\pi_{control}$) with an improvement at Month 6 in blinded evaluator's GAIS on the side treated with Radiesse (π_{test}) and on the side treated with Restylane ($\pi_{control}$).

The hypothesis on the secondary effectiveness endpoint and the corresponding analysis will be similar to that specified for the primary effectiveness analysis, however, using a less conservative margin of Δ = 0.15 (or 15%). This analysis will be of exploratory nature without any inferential considerations.

[redacted]

12.4.3 Safety Endpoints

The assessment of safety will be based mainly on the frequency of AEs and SAEs. Only treatment-emergent AEs will be summarized for each treatment group (as applicable) by the incidence of at least one event, the number of events, and the incidence using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms within the system organ classes (SOCs).

Safety endpoints and/or variables with continuous outcomes will be analyzed using descriptive summary statistics including the number of non-missing observations, mean and standard deviation, median, upper and lower quartiles, minimum and maximum for values and changes from baseline. Categorical safety data (e.g. laboratory parameters with reference to normal ranges) will be analyzed using frequency tables and, if applicable, shift tables.

12.4.4 Other Endpoints

Other endpoints and/or variables will be analyzed strictly in an exploratory manner without any inferential considerations.

[redacted]

Baseline and demographic characteristics will be summarized by appropriate descriptive statistics (n, mean, standard deviation, median, range). Concomitant medications will be listed and summarized by Anatomical Therapeutic Chemical (ATC) class and World Health Organization Drug Dictionary (WHODD) preferred term.

12.4.5 Other Statistical/Analytical Issues

12.4.5.1 *Significance Level and Power*

Significance level and power was described in Section 12.1 Determination of sample size.

12.4.5.2 *Expected Dropout Rate*

Expected dropout rate was described in Section 12.1 Determination of sample size.

12.4.5.3 *Planned Analyses and Early Termination of Study*

Statistical analyses will be performed when all subjects reach the 6 Month post initial injection time point. Primary effectiveness variable, secondary effectiveness variables and AE data will be analyzed using the snapshot of data for the first 6 months. A Statistical and a Clinical Study Report will be generated for the aforementioned analysis. They will be amended by a description and discussion of the analyses performed when all subjects have completed the study. For further details on which tables are produced for the Clinical Study Report and which for the amendment, please refer to the SAP.

No examination for early termination is planned.

12.4.5.4 *Discontinuations and Missing Data*

Besides the analyses based on observed data, additional sensitivity analyses for primary and secondary effectiveness endpoints will be carried out with missing data imputed using single value imputation methods. Imputations will be performed until Month 6.

Missing effectiveness data and missing safety data will be imputed as follows:

Effectiveness:

Worst Case Scenario (WCS):

- For the WCS method, missing post-baseline data for Radiesse treatment group will be imputed as non-responders, while missing post-baseline data for Restylane treatment group will be imputed as responders. As a result, the WCS is considered a conservative imputation method because missing values from the control are imputed as responders while missing values from the treatment are imputed as non-responders. The WCS will be used for sensitivity analysis.

Further imputation methods will be described in the SAP.

Safety:

Each medication/therapy will be allocated unambiguously either to previous medications or to concomitant medications.

- If stop date is before start of treatment: Previous medication
- If the stop date is at or after start of treatment or ongoing is checked: Concomitant medication
- Otherwise, if the stop date is missing or partially given:
  - Partial stop date available: Previous therapy if the latest possible stop date is before start of treatment; Concomitant therapy if the latest possible stop date is at or after start of treatment
  - If the stop date is completely missing: Concomitant therapy

Each finding will be allocated unambiguously either to medical history or to concomitant diseases.

- If the stop date is before start of treatment: Medical history
- If the stop date is at or after start of treatment or ongoing (even if it refers to a cut-off point before start of treatment) is ticked: Concomitant disease
- Otherwise, if the stop date is missing or partially given:
  - Partial stop date available: Medical history if the latest possible stop date is before start of treatment; Concomitant disease if the latest possible stop date is at or after start of treatment
  - Stop date is completely missing for findings coded as “Surgical and medical procedures”: Medical history
  - Stop date is completely missing for other findings: Concomitant disease

For AEs, imputation of missing start or stop dates will follow the steps below:

- If the start date (and time, if applicable) is partially missing but implies start before start of treatment or after date of final examination, the AE will be considered as Non- Treatment Emergent Adverse Event (TEAE).
- If the start date (and time, if applicable) is partially missing and possibly after start of treatment and before or after date of final examination, will be considered as TEAE.

AEs with completely missing onset dates will be considered treatment emergent; no estimation of the dates will be performed.

13 DATA HANDLING AND RECORDKEEPING

Data required according to this protocol is to be recorded in the web-based eCRFs (electronic data capture system eClinicalOS). All users who will enter data into the eCRF will be previously trained in the Training Database. After the successful completion of the training all participants will complete the Training Record Form which will be a prerequisite for the access to the eCRF, and sent to Kuntuo Data Management related staff (or Kuntuo's CRA). By signing and dating the eCRF, 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 eCRF.

All eCRF data collection will be performed through a secure web portal and all authorized personnel with access to the Electronic Data Capture (EDC) system must use personal credentials (username and password) to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

For the duration of the trial, the investigators will maintain complete and accurate documentation including but not limited to subject medical records, study progress records, laboratory reports, electronic case report forms, signed informed consent forms, device accountability records, and correspondence with the EC, monitor and Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the study. Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the sponsor, reviewing committees, or the core lab, should have all subject identifiers removed and replaced with the subject number.

All data required by this clinical study protocol are to be entered into a validated database.

If corrections in the subject diary or subject scales 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 CD/DVD, data clarification forms, and any associated subject-related source data

(5) Signed informed consent forms

(6) Copies of all direct correspondence with the EC, with the regulatory authority(ies), and with the sponsor

(7) Copies of laboratory normal ranges and methods

(8) Copies of investigational product 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 required retention period. The investigator/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 PROTOCOL DEVIATIONS AND AMENDMENTS

14.1 Protocol Deviation

Investigators will adhere to the protocol which has been agreed between Principal Investigators and the Sponsor and approved in writing by the EC consulted by the head of the investigational site.

Investigators will not deviate from or alter the protocol without written agreement between the Principal Investigator (PI) and the Sponsor and written approval by the EC based on prior review. Exceptionally, in case of urgent clinical need such as to minimize emergent risk to a subject, Investigators may deviate from the protocol without written agreement between the PI and the Sponsor and written approval by the EC based on prior review.

Investigators must document all deviations from the protocol using the Protocol Deviation (PD) Form from the subject-specific eCRF for whatever reason.

Only in case a deviation occurred due to urgent clinical need such as to minimize emergent risk to a subject, the Investigator will document the rationale for the deviation for immediate submission to the head of his/her investigational site and retain a copy and document the deviations from the protocol using the PD Form from the subject-specific eCRF. If the Investigator proposes that the protocol be amended, the Investigator may recommend changes to the sponsor. The sponsor will determine if it is appropriate to amend the protocol at which time the protocol will be reviewed by all site ECs for approval and use throughout the study.

In the event that an Investigator does not comply with Clinical Study Agreement or protocol, the Sponsor will be notified of the site’s non-compliance.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor’s monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator
- Telephoning the investigator
- Corresponding with the investigator

Repeated non-compliance with the signed agreement, the protocol or any other conditions of the study may result in further escalation in accordance with the Sponsor’s written procedures including securing compliance or, at its sole discretion; Sponsor may terminate the investigator's participation in the study.

14.2 Protocol Amendments

Approved protocol amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the EC of the protocol amendment (administrative changes) or obtaining EC's approval of the protocol amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the protocol amendment.

Acknowledgement/approval by the EC of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must also be provided to the Sponsor.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents for study-related monitoring, audits, EC review, and regulatory inspections.

Subjects providing informed consent agree to allow Sponsor or designee access and copying rights to pertinent information in their medical records concerning their participation in this study. The Investigator will obtain, as part of the informed consent, permission for study monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

16 FINANCE AND INSURANCE

Merz will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study. The terms of the insurance will be kept in the study files.

17 CLINICAL STUDY REPORT

A Clinical Study Report containing effectiveness and safety analyses will be generated after all subjects have completed the Month 6 visit. It will be amended by a description and discussion of the analyses performed when all subjects have completed the study. The content of the clinical study report and its amendment will meet the requirements of the Center of Medical Device Evaluation (CMDE).

18 CONFIDENTIALITY

18.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

18.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or IEC, may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

18.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- Name, address, telephone number and e-mail address;
- Hospital or clinic address and telephone number;
- Curriculum vitae or other summary of qualifications and credentials; and
- Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information.

Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

All material, information (oral or written) and unpublished documentation provided to the Investigator (or any action carried out by the company on their behalf), are exclusive property of the Sponsor.

These materials or information (both global and partial) cannot be given or disclosed by the Investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of the Sponsor.

The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

19 PUBLICATION POLICY

The institution and investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of Merz North America, Inc.

20 TASKS AND RESPONSIBILITIES

20.1 Responsibilities of the Investigator(s)

The Investigator will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator's responsibility to obtain written informed consent from subjects prior to inclusion in the study, and to record all data pertinent to the investigation. She/he will ensure that the information reported in the DCF is precise and accurate.

The Investigator or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the Subject of all pertinent aspects of the study including the written information. All subjects should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a subject's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the subject.

20.2 Responsibilities of the Sponsor(s)

The Sponsor of the study is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The Sponsor is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

21 REFERENCES

1. Jacovella PF. Calcium hydroxylapatite facial filler (Radiesse): indications, technique, and results. Clin Plast Surg. 2006 Oct; 33(4):511-23.

2. Glogau RG. Aesthetic and anatomic analysis of the aging skin. Semin Cutan Med Surg. 1996 Sep; 15(3):134-8.

3. Loghem JV, Yutskovskaya YA, Philip Werschler W, et al. Calcium hydroxylapatite: over a decade of clinical experience. J Clin Aesthet Dermatol. 2015 Jan; 8(1):38-49.

4. SUMMARY OF SAFETY AND EFFECTIVENESS DATA. Radiesse (Injectable Dermal Filler). http://www.accessdata.fda.gov/cdrh_docs/pdf7/k070090.pdf

5. Smith S, Busso M, McClaren M, et al. A randomized, bilateral, prospective comparison of calcium hydroxylapatite microspheres versus human-based collagen for the correction of nasolabial folds. Dermatol Surg. 2007 Dec; 33 Suppl 2:S112-21; discussion S121.

6. Bass LS, Smith S, Busso M, et al. Calcium hydroxylapatite (Radiesse) for treatment of nasolabial folds: long-term safety and efficacy results. Aesthet Surg J. 2010 Mar; 30(2):235-8.

7. Wu Y, Sun N, Xu Y, et al. Clinical comparison between two hyaluronic acid-derived fillers in the treatment of nasolabial folds in Chinese subjects: BioHyalux versus Restylane. Arch Dermatol Res. 2016 Apr; 308(3):145-51.

8. Newcombe RG. Improved confidence intervals for the difference between binomial proportions based on paired data. Statistics in medicine. 1998 Nov 30;17(22):2635-50.

22 APPENDICES

Appendix 1 Instructions for Use of Radiesse®

Appendix 2 Instructions for Use of Restylane®

DECLARATION OF INVESTIGATOR

Study name: Evaluation of the Effectiveness and Safety of Radiesse for the Correction of Nasolabial Folds

Study protocol number: M900311004

I agree to the content as follow:
I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations, and according to the protocol.

Accurate records of all data will be requested in case report form (CRF), complete clinical study report on time.

Medical devices for study be used in the clinical trials, complete and accurate recording of information for receiving and using of medical device in the process of clinical trials, and save the record.

Allow the monitor, auditor authorized by sponsor or and regulators to monitor, audit and inspection.

Strictly implement the clinical trials contract/term of an agreement signed by the parties.

I have read this protocol in its entirety, including the declaration above and agree to all of the above content.

Opinion of Sponsor

Signature(stamp): _____ Date: _____ (Day Month Year)

Opinion of Investigator

Signature: _____ Date: _____ (Day Month Year)

Opinion of Medical Device Clinical Trial Institution

Signature(stamp): _____ Date: _____ (Day Month Year)