1 TITLE PAGE

NCT04647721, redacted
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Evaluation of the Effectiveness and Safety of Radiesse for the Correction of Moderate to Severe Nasolabial Folds

Trial Identifier:	M900311009
Version Date:	27-NOV-2020, version 2.0
Investigational Medical Device (generic name):	RADIESSE® or Radiesse® (calcium hydroxylapatite injectable implant)
Specification:	1.5mL/syringe
Product Code Information:	8071M16
Indication:	Correction of moderate to severe nasolabial folds
Category of Investigational Medical Device:	Type III medical device that needs clinical trial approval Yes ☐ No ☒ Similar products in China Yes ☐ No ☒
Clinical Trial Institution:	[redacted] China
Lead/Coordinating investigator:	[redacted]
Trial Design:	Prospective, 48-week, randomized, multicenter, split-face, active-comparator, blinded [redacted] trial
Sponsor:	Merz North America, Inc. [redacted]
Legal Agent Information:	Merz Pharma China, Ltd.
Contract Research Organization:	[redacted]

Document References (For Internal Use Only)	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2 SYNOPSIS

Title of Trial	Evaluation of the Effectiveness and Safety of Radiesse for the Correction of Moderate to Severe Nasolabial Folds
Trial Identifier	M900311009
Investigative Sites	This trial will be conducted at approximately seven investigative sites in China.
Investigational Medical Device (generic name)	RADIESSE® or Radiesse® (calcium hydroxylapatite (CaHA) injectable implant)
Comparator Medical Device (generic name)	Restylane® (hyaluronic acid (HA) dermal filler gel)
Indication	Correction of moderate to severe nasolabial folds (NLFs)
Objectives	Effectiveness: To demonstrate non-inferiority of Radiesse (CaHA) to Restylane (HA) following subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as NLFs. Safety: To evaluate the incidence and type of adverse events and serious adverse events.
Effectiveness Evaluation	All endpoints will be assessed separately for the Radiesse and Restylane treatments, if not otherwise specified. *Primary endpoint* – Change from baseline to Week 24 after last injection on the Wrinkle Severity Rating Scale (WSRS) [redacted]. *Secondary endpoints* – Proportion of subjects with any improvement, defined as a rating of + 1, + 2, or + 3, on the Investigator Global Aesthetic Improvement Scale (iGAIS) for each NLF at Week 24 after last injection, as assessed by the treating investigator. – Proportion of subjects with any improvement, defined as a rating of + 1, + 2, or + 3, on the Subject Global Aesthetic Improvement Scale (sGAIS) for each NLF at Week 24 after last injection, as assessed by the masked subject.
Safety Evaluation	*Secondary endpoint* – Incidence of treatment-emergent adverse events related to Radiesse, as reported by the treating investigator throughout the trial.
Trial Design Overview and Methodology	This is a 48-week, prospective, randomized, multicenter, split-face, active-comparator, blinded [redacted] trial designed to evaluate the effectiveness and safety of Radiesse compared to Restylane for the correction of moderate to severe NLFs in healthy adults. Subjects will be enrolled from participating investigative sites in China. [redacted]

	[redacted] After a maximum 10-day screening period, the planned trial duration for individual subjects is 48 weeks (± 7 days) after last injection.
Number of Trial Subjects	Approximately 118 subjects will be randomized.
Main Inclusion/ Exclusion Criteria	Key inclusion criteria are: [redacted] Has symmetrical NLFs, with the same WSRS score of 3 or 4 (moderate or severe) for both right and left NLFs [redacted]. Is ≥ 22 and ≤ 65 years of age. Is willing to abstain from all other aesthetic treatments on ANY part of the face, including but not limited to injectable fillers, implants, neurotoxin, skin peels, laser treatments, surgical treatments, etc. for the trial's duration. Key exclusion criteria are: Has an acute inflammatory process or active infection at the injection site (e.g., skin eruptions such as cold sores, cysts, pimples, acne, rosacea, eczema, rashes, hives, or abscesses). Has received mid- and/or lower-facial region treatments with any dermal filler [redacted] Has received facial dermal therapie [redacted]. Had prior surgery in the mid- and/or lower-facial area, including the NLFs, or has a permanent implant or graft in the mid- and/or lower-facial area that could interfere with effectiveness assessments [redacted]

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ANCOVA	Analysis of covariance
ASADE	Anticipated serious adverse device effect
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BDRM	Blind data review meeting
BMI	Body mass index
BUN	Blood Urea Nitrogen
CaHA	Calcium hydroxylapatite
CD	Compact disc
Chinese GCP	China's Good Clinical Practice for Medical Devices
CI	Confidence interval
CMDE	Center of Medical Device Evaluation (China)
CRF	Case report form
CRO	Contract research organization
CTP	Clinical trial protocol
[redacted]	
DVD	Digital versatile disc
eCRF	Electronic case report form
EDC	Electronic data capture
EN ISO	International Organization for Standardization (ISO) as adopted by the European Union (EN)
EOT	End of Trial
EU	European Union
FAS	Full analysis set
[redacted]	
FDA	Food and Drug Administration (USA)
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GSP	Good Supply Practices per China medical device distributors
HA	Hyaluronic acid

Abbreviation	Definition
HIV	Human immunodeficiency virus
IEC	Independent ethics committee
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFU	Instructions for use
iGAIS	Investigator Global Aesthetic Improvement Scale
IMD	Investigational medical device
IRB	Institutional Review Board
[redacted]	
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NHFPC	National Health and Family Planning Commission of the People's Republic of China
NLF	Nasolabial fold
NMPA	National Medical Products Administration (China)
PD	Protocol deviation
PEV	Primary endpoint visit
PHI	Protected health information
PLLA	Poly L-lactic acid
PPS	Per protocol set
[redacted]	
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software®
SES	Safety evaluation set
sGAIS	Subject Global Aesthetic Improvement Scale
SMO	Site management organization

Abbreviation	Definition
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Tu	Touch-up (In this CTP, used to refer to touch-up injection.)
Tx	Treatment (In this CTP, used to refer to initial injection.)
USA	United States of America
USADE	Unanticipated serious adverse device effect
USP	United States Pharmacopeia
UV	Ultraviolet
VAR	SAS variable
WSRS	Wrinkle Severity Rating Scale

Definitions of Terms

Synonymous terms	
Clinical trial protocol	Clinical investigation plan
Effectiveness	Clinical performance
Investigational medical device	Investigational device or Investigational product
Trial	Investigation or study
Device deficiency	Technical complaint

Sponsor and Investigator Information

Sponsor Information

Sponsor Name	Merz North America, Inc.
Sponsor Address	6501 Six Forks Road, Raleigh, North Carolina 27615 USA
Sponsor Contact Information	Phone: [redacted]
Agency Name, Address, Contact Information, and Qualified Documents Related	Merz Pharma China, Ltd. Room 608, Tomson Financial Building, 710 Dong Fang Road, Shanghai, China, 200122 Phone: [redacted]

[redacted] **List of clinical trial institutions** [redacted]

Clinical Trial Institution Name
Peking University First Hospital
Zhejiang Provincial People's Hospital
The Third Affiliated Hospital of Sun Yat-Sen University
Renmin Hospital of Wuhan University

[redacted]

Clinical Trial Institution Name	[redacted]
Zhongda Hospital Southeast University	
Peking University Third Hospital	
Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine	

Responsibilities of All Parties

Sponsor's Statement

The sponsor should perform duties according to Article 6 of "State Food and Drug Administration National Health and Family Planning Commission" (No. 25, People's Republic of China, National Health and Family Planning Commission, National Medical Products Administration). The clinical trial institution and the investigators should perform duties according to Article 7 of "State Food and Drug Administration, National Health and Family Planning Commission" (No. 25, People's Republic of China, National Health and Family Planning Commission, National Medical Products Administration).

Investigator's Statement

I agree that:

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol.
2. I will record all required data accurately and in a timely manner on the Case Report Form (CRF) and complete the final report of the clinical trial on time.
3. The investigational medical devices will be used only for this clinical trial, and the receipt and use of the investigational medical devices will be recorded completely and accurately, and the records will be retained during the process of the clinical trial.
4. The monitor and verifier, as authorized or designated by the sponsor, and the regulatory authorities are allowed to conduct monitoring, verification, and inspection for the clinical trial.
5. The clinical trial should be conducted in strict compliance with contract/articles of agreement signed by all parties.

I have already read the clinical trial protocol, including the above statement, and I fully agree to all the above requirements.

Comments from the sponsor:

Signature (stamp):

Date (MM/DD/YYYY):

Comments from the investigator:

Signature (stamp):

Date (MM/DD/YYYY):

Comments from the medical device clinical trial institution:

Signature (stamp):

Date (MM/DD/YYYY):

5 ETHICS

5.1 Ethical Conduct of the Trial

This trial will be performed in accordance with the principles outlined in the Declaration of Helsinki and in compliance with the standards for Good Clinical Practice (GCP) described in International Organization for Standardization as adopted by the European Union (EN ISO) 14155 and in China's GCP for Medical Devices (Chinese GCP; No. 25 Order of China National Medical Products Administration (NMPA) and National Health and Family Planning Commission of the People's Republic of China (NHFPC)), Notice on Issue of Guidelines for the Design of Medical Device Clinical Trials (CFDA 2018 No. 6), and any applicable regional or national laws and regulations. The trial will adhere to all applicable subject privacy requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the trial.

All required approvals, favorable opinions, or additional requirements of the appropriate Independent Ethics Committee (IEC), Institutional Review Board (IRB), or other regulatory authority will be obtained prior to initiation of the trial.

The investigator and all trial personnel will conduct the trial in compliance with this protocol. The investigator will ensure that all personnel involved in the conduct of this trial are qualified to perform the assigned trial responsibilities. Investigators will adhere to all applicable trial-reporting requirements.

5.2 Informed Consent

A subject will provide verbal and written informed consent to the investigator (or authorized designee) according to the provisions set forth in the Declaration of Helsinki, EN ISO 14155 (Chapter 4.7), and Chinese GCP. The obligations of the investigator are set forth in the clinical trial protocol (CTP), the Declaration of Helsinki, EN ISO 14155, Chinese GCP, and local Chinese requirements governing medical research and experimentation on humans. Consent must be obtained from every subject prior to the initiation of any screening or trial procedures. The informed consent process must be traceable from the available documentation. At a minimum, this documentation should include information about when the subject was first informed about the investigation and who supplied the information.

If the informed consent form (ICF) is amended during the trial, the investigator and the contract research organization (CRO) must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IEC/IRB and use of the amended form. Ongoing subjects will be required to re-confirm consent by signing the amended form.

One original, and any amended, signed and dated ICF(s) must be retained at the investigative site; a second original signed and dated ICF(s) must be given to the subject.

During the trial, the subject will be informed if information becomes available that may be relevant to the subject's willingness to continue participation in the trial. In the case of an adverse event (AE) or poor tolerability to the trial device(s), the subject should inform the investigator, who will then make a judgment whether continuing in the investigation serves the subject's best interest. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

5.3 Subject Privacy

The subject will be informed of procedures to protect subject privacy. The CRO, the sponsor, or an authorized vendor will process subject data only in accordance with the data-protection provisions set forth in the German Federal Data Protection Act (Bundesdatenschutzgesetz), specifically in the version applicable as of 25-MAY-2018, and in Regulation (European Union or EU) 2016/679 (General Data Protection Regulation). Informed consent on data processing will be obtained in writing directly from the subject before recording of any data. Authorization to use and disclose health information that could identify the subject (referred to as protected health information or PHI) will be obtained in writing directly from the subject before recording of any data. Recorded data will be pseudonymized before transferring to authorized individuals. The investigator will maintain source documents that link unique subject numbers with subject names (e.g., in case of emergencies).

[redacted]

5.4 Confidentiality of Subject Information

Subject pseudo-anonymity is to be maintained during the trial. Subjects will be identified by a unique, assigned number on all trial documentation. Health information that could identify the subject (i.e., PHI) must be maintained in strict confidence by the investigator, to the extent permitted by applicable laws and regulations. Subjects must allow PHI to be disclosed to the sponsor and anyone working on behalf of the sponsor, the IRB/IEC, or regulatory authorities.

Confidentiality will also be maintained for any medical information obtained from the subject during trial participation. At a subject's request, the subject's medical information may be provided to other appropriate medical personnel.

If the results of the investigation are published, the subject's identity will remain confidential.

5.5 Insurance

The trial sponsor will provide insurance. From the beginning of the investigation until its termination, each subject is insured against any health impairment occurring as a result of participation in the investigation in accordance with Chinese laws and regulations.

The subject will be informed by the investigator and through the ICF about the existence of this insurance and the resulting obligations. The insurance conditions will be distributed to the subject if requested or if required by local Chinese requirements.

Any medical deviation from the CTP that is deemed to have occurred through the subject's own fault is not covered by this insurance.

Relatedness of potential injury to trial devices and/or procedures should be assessed by the treating investigator. The sponsor is usually not liable for injuries or deaths that occur solely because of the subject's pre-existing medical condition(s) or from diagnostic or therapeutic measures not specifically required by the agreed CTP. The sponsor is also usually not liable for events resulting from negligence of the investigator, trial personnel, and/or CRO, including failure to act according to EN ISO 14155 principles and/or Chinese GCP or to comply strictly with the agreed CTP.

The terms of the insurance will be kept in the trial files.

5.6 Financing

The financial aspects of the investigation will be documented in an agreement between the sponsor, the CRO, and each investigator or any other involved party, and must be confirmed in writing before the investigation commences.

6 INTRODUCTION

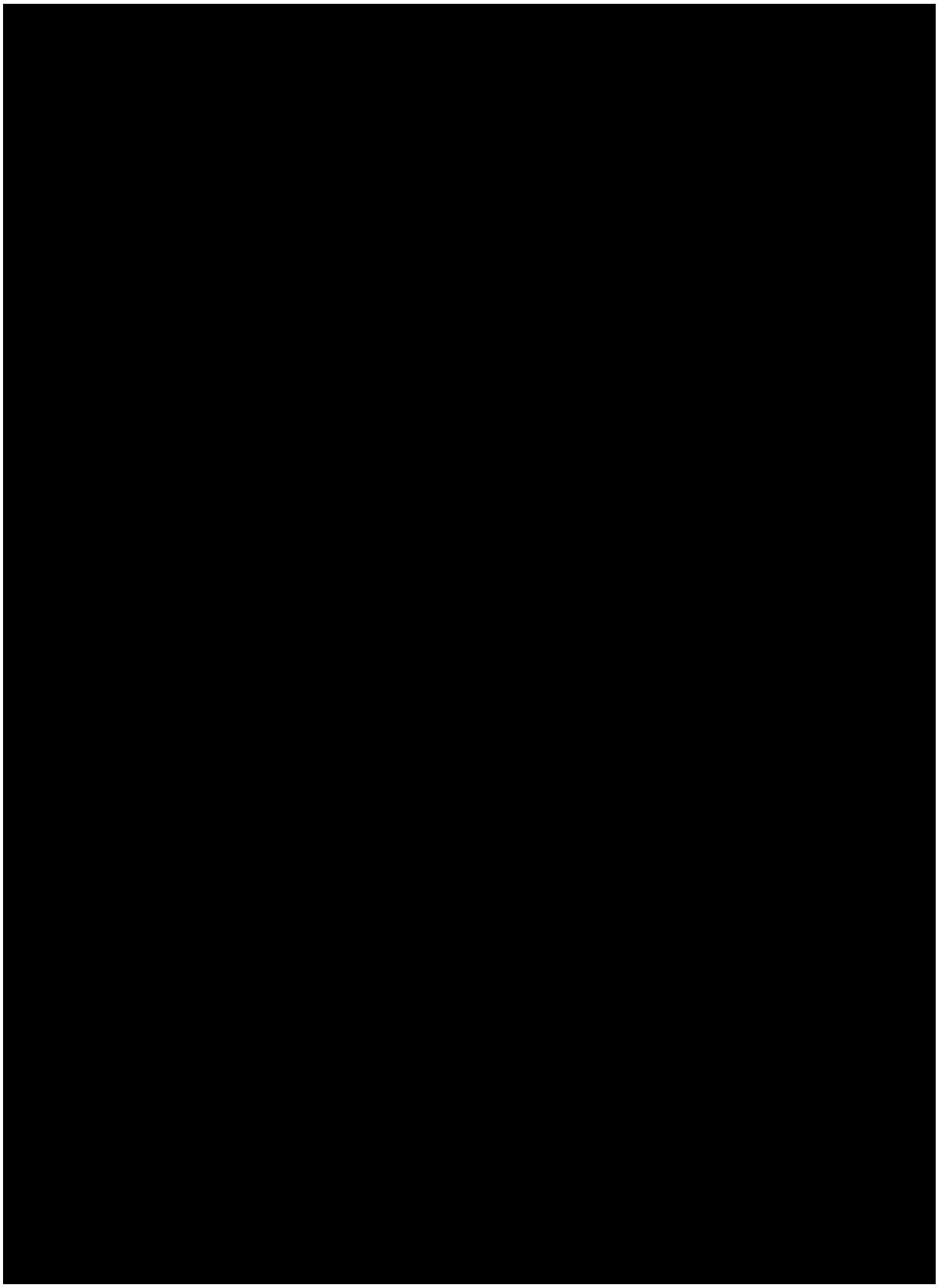
6.1 Background

As part of the natural aging process, and accelerated by exposure to sunlight, poor nutritional habits, smoking, genetic patterns, and other factors, the skin (particularly the skin of the face) begins to lose its youthful appearance with the passage of time. The changes associated with aging of the face are characterized by degeneration and loss of collagen and elastic fibers of the skin, as well as diminished volume of fat, muscle, and bone. The most common signs that result from facial aging include visibility of bony landmarks, perioral vertical rhytids, ptosis of the oral commissures and brow, thinning of the lips, and prominence of facial wrinkles and folds, specifically nasolabial folds (NLFs) [1-8].

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 aging 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 subjects requiring extensive aesthetic changes. However, injectable, soft-tissue fillers are increasingly becoming an acceptable option for the correction of selected, specific signs of aging, including deep NLFs, marionette lines, and perioral wrinkles. Over the last several years, injectable fillers have become an integral part of cosmetic therapy [8].

Multiple published reports have documented the use of dermal fillers, including calcium hydroxylapatite (CaHA) gel and hyaluronic acid (HA), to improve the appearance of NLFs [9-11]. Both CaHA gel and HA injectable products are biodegradable fillers and have been shown to exhibit excellent safety profiles. [redacted]

[redacted]



6.2 Trial Rationale

Radiesse first received EU approval in 2003 for plastic and reconstructive surgery, including deep dermal and subdermal soft-tissue augmentation of the facial area [14]. In 2006, Radiesse received USA FDA approval for the correction of moderate to severe facial wrinkles and folds, such as NLFs, and for the correction of mid-facial lipoatrophy in people with human immunodeficiency virus (HIV). Marketed in more than 50 countries [14], Radiesse has become a very effective filler agent, providing soft-tissue augmentation for many areas of the face, while maintaining an excellent safety and patient satisfaction profile.

6.2.1 Justification of Proposed Trial Design and Primary Effectiveness Endpoint

This current trial is designed to demonstrate the effectiveness and safety of Radiesse in a split-face trial that compares this CaHA dermal filler to an HA dermal filler, Restylane, for treatment of NLFs. The safety and effectiveness of Radiesse for use as a soft-tissue filler in the NLFs, hands, and face has been demonstrated in other studies, resulting in extensive use worldwide [10-15]. Although Radiesse, as a CaHA, differs from HA fillers in its ultimate mechanism of action, proposed use of a split-face trial design and an active comparator follows China's Center of Medical Device Evaluation (CMDE) guidelines for NLF treatment with dermal fillers. The primary effectiveness endpoint has been chosen to demonstrate that Radiesse will be non-inferior to Restylane for correction of moderate to

severe NLFs when assessed at Week 24. [redacted] he current proposed trial design and trial duration of 48 weeks are expected to further support the safe and effective use of Radiesse for treatment of NLFs in adults.

6.3 Potential Benefits and Risks

The potential benefit of Radiesse is soft-tissue augmentation and correction of facial wrinkles and folds, such as NLFs, as well as an improved overall aesthetic impression of the face. [redacted]

The potential risks associated with Radiesse are expected to be similar to other CaHA fillers used worldwide and HA-dermal fillers that are currently commercially available in China and other markets. As described previously, Radiesse has been evaluated extensively in worldwide studies. The safety and effectiveness of Radiesse have been demonstrated consistently on an international scope during both rigorous randomized controlled trials and worldwide commercial experience [11-15].

[redacted]

Adverse events have been reported in post-market surveillance with post-approval use of Radiesse. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship. The following events have been identified due to a combination of their seriousness, frequency of reporting, or potential causal relationship with Radiesse: cystic acne, milia, skin dryness (i.e., rough facial skin, exfoliation), tenderness, pain, infection,

shivering, lymphadenopathy, burning sensation, injection-site sore/warmth, induration, fever, cellulitis, impetigo, loss of effect, product displacement/migration, allergic reaction, anaphylaxis, hives, rash, pruritus, urticaria, angioedema, inflammation, necrosis, granuloma, blister, vesicle, papule, lump/bump (visible and/or palpable material) or nodules, erythema, ecchymosis/bruising, skin discoloration, hyper- or hypo-pigmentation, pustule, skin pallor, hair loss, tingling, numbness, hypoesthesia, paresthesia, ptosis, headache, edema/swelling, asymmetry, abscess, temporary scabs, needle marks, urticaria, transient bleeding, hematoma, telangiectasia, herpetic infection (including herpes simplex and herpes zoster), hematoma, blanching, blistering, headache/cephalgia, dizziness, flu-like symptoms, Guillain-Barre syndrome, tachypnea, ischemic reaction, lymphoid hyperplasia, nausea, vomiting, pericarditis, scarring, sensitivity to cold, vascular occlusion/obstruction, vascular compromise, embolization, necrosis, ocular ischemia, diplopia, visual impairment/blindness, facial muscle paralysis, Bell's palsy, impairment of the otorhinolaryngological system (e.g., nasal congestion, oropharyngeal pain, dysgeusia, rhinorrhea, epistaxis, sinusitis, transient hearing loss) mastication pain, muscle twitching, muscle injury, anxiety caused by trypanophobia and disappointment (i.e., due to lack of or reduced product performance, decreased firmness/response, undesirable aesthetic effect, injection-site discharge, injection-site indentation, superficial vein prominence, patient dissatisfaction) [redacted]).

Vascular occlusion, resulting in ischemia/necrosis, and vision disturbances, including blindness, have been reported following injection of soft-tissue fillers in the face especially when injected in the nose, glabella, periorbital areas, NLFs, and cheek; time to onset may range from immediate to a few weeks following injection. Vascular compromise may occur due to an inadvertent intravascular injection or as a result of vascular compression associated with implantation of any injectable product. This condition may manifest as blanching, discoloration, necrosis, or ulceration at the implant site or in the area supplied by the blood vessels affected, or rarely, as ischemic events in other organs due to embolization. Isolated, rare cases of ischemic events affecting the eye, leading to visual loss, and affecting the brain, resulting in cerebral infarction, following facial aesthetic treatments have been reported.

Additional information on product- and treatment administration-related contraindications, warnings, and precautions can be found in the applicable investigational device and comparator device IFUs [redacted]

[redacted]

7 TRIAL OBJECTIVES AND ENDPOINTS

7.1 Objectives

Effectiveness

The primary objective is to demonstrate non-inferiority of Radiesse (CaHA) to Restylane (HA) following subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as NLFs.

Safety

The safety objective includes an evaluation of the incidence and type of adverse events (AEs) and serious adverse events (SAEs).

7.2 Endpoints

All endpoints will be assessed separately for Radiesse and Restylane treatments, if not otherwise specified.

[redacted]

7.2.1 Effectiveness Endpoints

7.2.1.1 Primary Effectiveness Endpoint

- Change from baseline to Week 24 after last injection on the Wrinkle Severity Rating Scale (WSRS)[redacted].

7.2.1.2 Secondary Effectiveness Endpoints

- Proportion of subjects with any improvement, defined as a rating of + 1, + 2, or + 3, on the Investigator Global Aesthetic Improvement Scale (iGAIS) for each NLF at Week 24 after last injection, as assessed by the treating investigator.

- Proportion of subjects with any improvement, defined as a rating of + 1, + 2, or + 3, on the Subject Global Aesthetic Improvement Scale (sGAIS) for each NLF at Week 24 after last injection, as assessed by the masked subject.

[redacted]

7.2.2 Safety Endpoints

7.2.2.1 Secondary Safety Endpoint

- Incidence of treatment-emergent AEs (TEAEs) related to Radiesse, as reported by the treating investigator throughout the trial.

8 CLINICAL INVESTIGATION PLAN

8.1 Overview of Trial Design

This is a 48-week, prospective, randomized, multicenter, split-face, active-comparator, blinded [redacted] trial designed to evaluate the effectiveness and safety of Radiesse compared to Restylane for the correction of moderate to severe NLFs in healthy adult subjects. Those enrolled will have symmetrical NLFs, with the same WSRS score of 3 or 4 (moderate or severe) for both right and left NLFs, as determined on live assessment [redacted].

[redacted]

Al [redacted] will be blinded to treatment assignment. [redacted] rimary effectiveness will be evaluated using the change from baseline to Week 24 after last injection on the WSRS [redacted].

Subjects who do not achieve at least 1-point improvement on the WSRS at Week 4 when compared to baseline, [redacted] will have a touch-up injection in [redacted] NLFs to achieve optimal correction (i.e., ≥ 1-point improvement). If a touch-up is performed, the same randomized product assigned for the initial injection must be used. [redacted]

[redacted]

[redacted]

Standard safety parameters, including documentation of AEs and SAEs, will be assessed. [redacted]

After a maximum 10-day screening period, the planned trial duration for individual subjects is 48 weeks (± 7 days) after last injection.

[redacted]

8.2 Discussion of Trial Design, Including the Choice of Control Groups

As detailed in Section 8.1, this is a 48-week, prospective, randomized, multicenter, split-face, active-comparator, blinded [redacted] trial designed to establish that Radiesse is safe and effective for the correction of moderate to severe NLFs by demonstrating non-inferiority to Restylane and by comparing the safety profiles of both products.

Active-controlled clinical studies are considered the standard for clinical investigations whenever proven effective treatments exist on the market for a given condition. A previous study of Radiesse with active HA comparators has demonstrated effectiveness and patient satisfaction for CaHA filler compared to HA in the treatment of NLFs [17]. Restylane will be utilized as the comparator in this proposed trial, as no other CaHA filler is currently marketed in China, and Restylane represents the best possible comparator.

[redacted] he trial duration of 48 weeks also represents a reasonable timeframe to assess delayed-onset and/or long-term AEs.

Since subject satisfaction is the primary goal of aesthetic medicine, subjects may undergo a touch-up treatment after initial injection to achieve optimal correction [redacted] herefore, the choice of active comparator is suitable for demonstration of treatment effectiveness.

9 TRIAL POPULATION AND RESTRICTIONS

9.1 Number of Subjects and Sites

Approximately 118 subjects will be randomized at up to seven investigative sites in China. Enrolled subjects will sign and date the ICF before any trial-related procedures are undertaken. At each of seven sites, the number of subjects treated should not exceed 20 to ensure a reasonable distribution of subjects across all investigative sites (see Section 13.1.2 for additional information).

Any treated subject who does not complete the trial will not be replaced.

Additional information regarding the estimation of sample size, including the numbers of randomized subjects projected for trial sites, is reported in Section 13.1. Further information related to subject randomization is provided in Section 13.2.

9.2 Selection of Subject Population

Assessment for eligibility criteria is based on the subject's medical records, an interview with the candidate subject, and investigator judgment. Selection criteria have been chosen to identify a suitable subject population to investigate the trial objectives and to minimize safety concerns in this population.

9.2.1 Inclusion Criteria

To be eligible for trial participation, each subject must meet all of the following criteria at screening (V1; Day −10 to 1) and/or baseline (V2; Day 1):

[redacted]

- Has symmetrical NLFs, with the same WSRS score of 3 or 4 (moderate or severe) for both right and left NLFs[redacted].
- Is ≥ 22 and ≤ 65 years of age.
- Is willing to abstain from all other aesthetic treatments on ANY part of the face, including but not limited to injectable fillers, implants, neurotoxin, skin peels, laser treatments, surgical treatments, etc. for the trial's duration.

[redacted]

[redacted]

9.2.2 Exclusion Criteria

Subjects meeting any of the following criteria at screening (V1; Day −10 to 1) and/or baseline (V2; Day 1) are not eligible to participate in the trial:

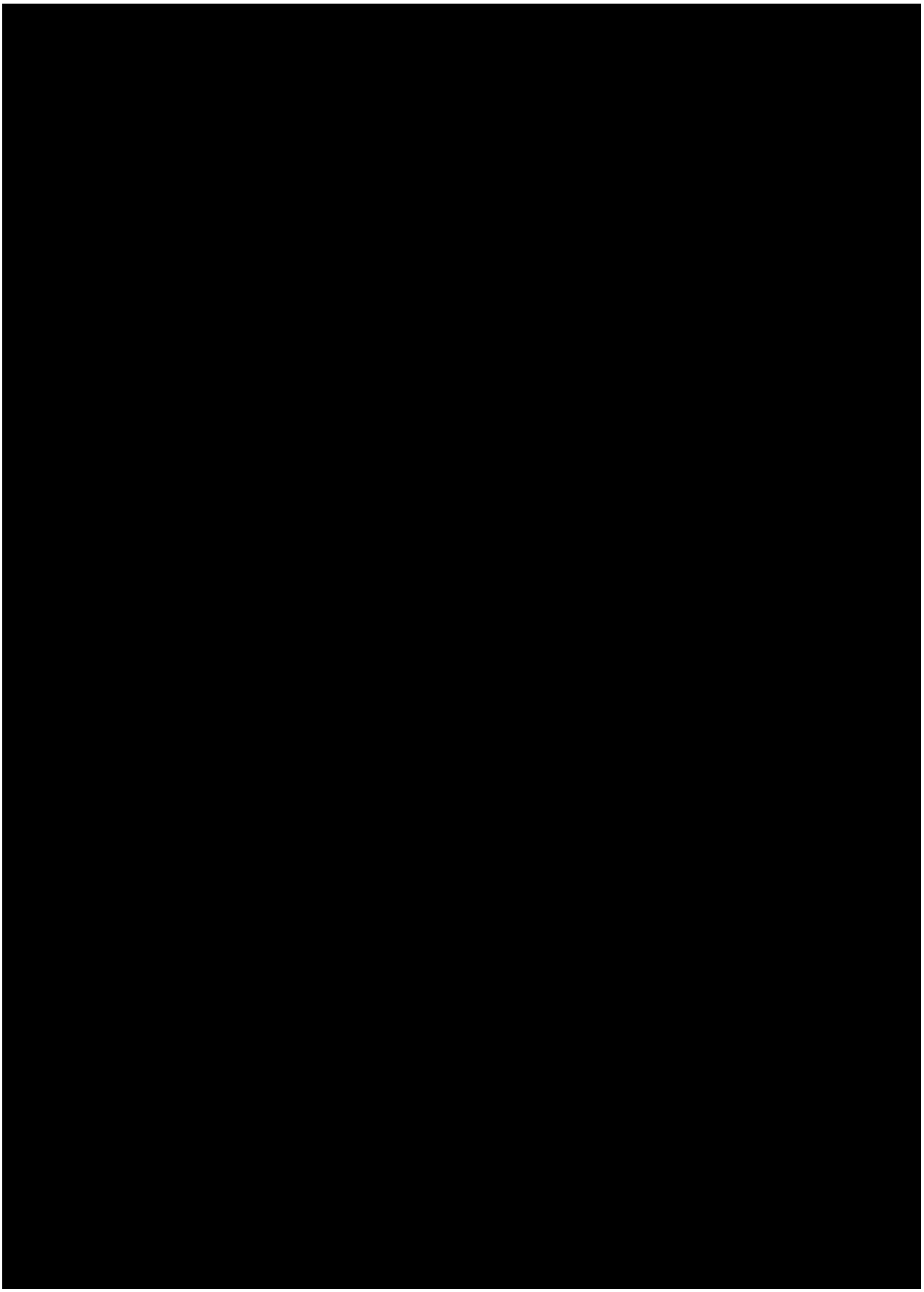
[redacted]

- Has an acute inflammatory process or active infection at the injection site (e.g., skin eruptions such as cold sores, cysts, pimples, acne, rosacea, eczema, rashes, hives, or abscesses).

[redacted]

- Has received mid- and/or lower-facial region treatments with any dermal fillers [redacted].
- Has received facial dermal therapie [redacted].
- Had prior surgery in the mid- and/or lower-facial area, including the NLFs, or has a permanent implant or graft in the mid- and/or lower-facial area that could interfere with effectiveness assessments. [redacted]

[redacted]



9.2.4 Subject Enrollment and Randomization

Subjects are considered to be enrolled once the ICF is signed and dated. Eligible subjects will be randomized at baseline (V2).

Screen failures are defined in Section 9.2.5.

9.2.5 Screen Failures

Subjects who provide informed consent but who do not meet eligibility criteria or who withdraw consent prior to being randomized will be defined as screen failures. The investigator will maintain all source documentation for all subjects who are considered screen failures. Minimal information will be collected in the electronic data capture (EDC) system for screen failures, such as date of informed consent, demographics, and reason for screen failure. Individuals who do not meet the criteria for participation in this trial (i.e., screen failure) may not be rescreened.

9.2.6 Removal of Subjects from Therapy or Assessment

9.2.6.1 Treatment Discontinuation

In the current trial design, potential reasons for discontinuation of treatment may include refusal by the subject to receive a required or recommended touch-up injection (i.e., necessary to achieve optimal correction) or a treating investigator's decision that the risk of continued treatment (i.e., touch-up injection) is greater than the subject's potential benefit.

If treatment is discontinued, the investigator will record the reason for treatment discontinuation in the trial records. The investigator may request that a subject discontinuing treatment continue to participate in the trial and complete all remaining visits and assessments for safety follow-up. For subjects who decline to continue trial participation after treatment discontinuation, additional information regarding subject withdrawal is provided in Section 9.2.6.2.

9.2.6.2 Subject Withdrawal or Discontinuation

Each subject will be followed to the end of trial, or until the sponsor decides to terminate the trial, whichever comes first. The only reasons a subject will not be followed for all scheduled visits include withdrawal of consent, continuous noncompliance with protocol requirements, or loss to follow-up (e.g., moving away from trial site; unresponsive to attempts to contact the subject). Additionally, the investigator can discontinue any subject, at any time, if medically necessary.

A subject has the right to withdraw from the trial at any time at his/her own request without any penalty or loss of benefits to which the subject is otherwise entitled. In cases of withdrawn consent, data collected until the date consent was withdrawn will be analyzed as recorded.

If a subject does not attend a required trial visit, the following actions will be taken:

- The site will make every reasonable attempt to contact the subject and reschedule the missed visit as soon as possible. Every effort to regain contact with the subject will be made (e.g., phone contact on different dates/times, registered mail). All contact attempts will be documented.
- If attempts to contact the subject are not successful, the subject will be considered lost to follow-up and discontinued from the trial.

The reason for the subject's discontinuation should be documented in the electronic case report form (eCRF). The investigator should make every attempt to complete the recommended follow-up assessments specified for the End of Trial (EOT) visit specified in the Schedule of Events (Section 11.1[redacted]) while fully respecting the subject's rights. If appropriate, according to local regulations, IEC/IRB and Competent Authorities should be informed.

If a non-serious AE is unresolved at the time of the subject's final trial visit, an effort will be made to follow the subject until the AE is resolved or stabilized, the subject is lost to follow-up, or some other resolution of the event occurs. The investigator should make every attempt to follow all SAEs/unanticipated serious adverse device effects (USADEs) to resolution. Information on pregnancy and the outcome for any female who becomes pregnant during the trial will be collected.

9.2.6.3 Provision of Care for Subjects after Trial Discontinuation

The investigator is responsible for ensuring the adequate and safe medical care of subjects during the trial. At the end of the trial or after subject discontinuation, the investigator will ensure that appropriate consideration is given to a subject's after-trial care. Subjects will be treated by their physician according to their medical condition and standard treatments in China. Additionally, the sponsor will follow all applicable local or international regulations and guidelines regarding follow-up care for subjects.

9.2.7 Suspension or Premature Termination of an Investigative Site

Trial participation by individual sites may be suspended or prematurely terminated by the sponsor. Reasons for the suspension or premature termination of sites include, but are not limited to, the following:

- Investigator request;
- Serious or persistent noncompliance with the protocol, local regulations, and/or Chinese GCP;
- Suspicion of fraud;
- Failure to accrue subjects at an acceptable rate; and/or
- Ethical issues.

The sponsor will provide the investigative site with written notification documenting the reason for suspension or premature termination. The sponsor will inform the responsible regulatory authority, as appropriate, and ensure the IEC/IRB is notified. If the suspension or premature termination was in the interest of safety, the sponsor will inform all other principal investigators.

In cases of temporary suspension at an investigative site, the sponsor will conduct an analysis of the reason(s) for suspension. After completing this analysis and implementing necessary corrective actions, a temporary site suspension may be lifted. The sponsor will inform the principal investigators, the IEC/IRB, and, where appropriate, the regulatory authority of the rationale, providing relevant data supporting this decision. Concurrence must be obtained from the IEC/IRB and, where appropriate, regulatory authorities before the investigative site resumes trial activities. If subjects were informed of the suspension, the principal investigator or authorized designee will inform them of the reasons for resumption.

In cases of premature termination, the investigator will conduct site-closure activities in accordance with all applicable sponsor, local, and international guidelines and regulations.

9.2.8 Suspension or Premature Termination of the Trial

Should the investigator, sponsor, the NMPA, or local regulatory authorities become aware of conditions arising during the conduct of this trial that may warrant the cessation of the trial, such action may be taken. Prior to such action, consultation between the sponsor, the investigator, and, as appropriate, the NMPA and/or local regulatory authorities will occur.

Reasons for the suspension or premature termination of the trial include, but are not limited to, the following:

- Anticipated benefit cannot justify the risk;
- New scientific data do not justify a continuation of the trial;
- Determination of a potential safety risk to subjects;
- Inadequate subject enrollment;
- Decision by the regulatory authority or IEC/IRB to suspend or terminate approval/ favorable opinion for the trial; and/or
- Sponsor decision.

If suspicion of an unacceptable risk to subjects arises during the trial or if instructed by the IEC/IRB or regulatory authorities, the sponsor will suspend the trial while the risk is assessed. If the analysis determines that implementing necessary corrective actions is sufficient, a temporary trial suspension may be lifted. If an unacceptable risk is confirmed, the sponsor will terminate the trial.

If the trial is suspended or prematurely terminated for any reason, the sponsor will inform all investigators and relevant regulatory authorities promptly of the trial suspension/termination and reason for the action, as detailed in Section 9.2.7. The investigator will conduct site-closure activities in accordance with all applicable sponsor and local/international guidelines and regulations.

9.2.9 End of Trial

The end of the trial is defined as when the database is closed for the final (Week 48 after last injection) analyses.

10 TRIAL DEVICES AND TREATMENT OF SUBJECTS

10.1 Description of Trial Devices

10.1.1 Investigational Medical Device - Radiesse

Radiesse injectable implant is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant. The principal component is synthetic CaHA suspended in a gel carrier that consists primarily of wate[redacted]

Radiesse is provided as a single use, non-pyrogenic device. Each unit contains a 1.5 mL/syringe of injection media in a pre-filled syringe. The investigational device will be supplied by the sponsor and will be marked for trial-specific clinical use only. [redacted] o not use if the expiration date has been exceeded. Do not re-sterilize the syringe or any of its separately packaged components (e.g., needle). In the event the package is opened or damaged, do not use and notify the sponsor immediately.

Radiesse injectable implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as NLFs. [redacted]

[redacted]

10.1.2 Comparator Device - Restylane

Restylane is a clear, transparent, and viscous modified sodium hyaluronate gel for facial-tissue augmentation by injection into the mid-dermis. Restylane contains a gel of modified hyaluronic acid (HA) 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 nonanimal origin.

Restylane is supplied in a disposable glass syringe at two volumes (0.5 mL/syringe and 1 mL/syringe) with a Luer-lock fitting. The contents of the syringe are sterile. Restylane is packaged with sterilized 29 gauge x 1/2 inch needle to be used for injection into the mid-dermis. The 0.5 mL/syringe package contains one glass syringe with Restylane gel and one needle. The 1 mL/syringe package contains one glass syringe with Restylane gel and two

needles. Restylane will be supplied by the trial sponsor and will be marked for trial-specific clinical use only. Restylane must be used prior to the expiration date printed on the package. It should be stored at a temperature of up to 25° C (77° F). Do not freeze. Protect from sunlight. Do not resterilize Restylane as it may damage or alter the product. Do not use if the package is damaged.

Restylane is intended to be used for facial-tissue augmentation by injection into the mid-dermis to correct moderate to severe NLFs. Restylane should be injected into the middle part of the dermis layer of the facial skin. This product is only intended for use as an intradermal implant, and should not be used for breast injection. Restylane will degrade gradually in the body, typically 6 to 12 months after injection. With degradation, the filler effect will disappear. Patients preferring to maintain the filler effect can receive follow-up injection when the filler effect disappears. [Note: No retreatment injection will be provided under this CTP.] As reported [redacted], the filler effect remains for longer than six months in the majority of patients as shown in the Chinese study, where the patients were injected in the NLFs.

[redacted]

[redacted]

10.3 Methods of Assigning Subjects to Treatment Groups

Subjects who complete all screening assessments and meet all eligibility criteria will be randomized 1:1 to one of the following groups prior to injection:

- Group 1: left NLF: Radiesse, right NLF: Restylane
- Group 2: left NLF: Restylane, right NLF: Radiesse

Care must be taken to follow the subject's randomization assignment, ensuring that the Radiesse and Restylane syringes are injected in the randomly assigned NLF (left NLF or right NLF). Accurate documentation of which product (Radiesse or Restylane) is injected into which NLF (subject's right or left) is of critical importance in this trial.

This information will remain in the subject's source documents and be made available for verification of the proper randomization sequence by the sponsor or designee during monitoring visits.

Additional methodological details regarding randomization are provided in Section 13.2.

10.4 Blinding Procedures

10.4.1 Blinding

[redacted]

To ensure that the subject-level blind is maintained, subjects will have their upper face masked or covered during initial and optional touch-up treatments. [redacted]

To ensure that sponsor and CRO personnel involved in data cleaning and analysis will remain blinded, the personnel involved in producing, implementing and monitoring the randomization will be different from the ones involved in data cleaning and analysis and obliged to confidentiality.

[redacted]

10.4.2 Planned Unblinding

[redacted] For trial personnel involved in data cleaning or analysis, the blind will not be broken until the blind data review meeting has convened, the statistical analysis plan (SAP) has been finalized, and the database has been closed. After the blind is broken, the statistical analysis of results will proceed, which will be documented according to GCP.

[redacted]

10.5 Trial Treatment

All protocol-specific criteria for the administration of trial treatment must be met and documented prior to administration of any trial treatment. [redacted] subjects will not be dispensed any

investigational material. Any noncompliant investigative site may be discontinued from the trial (Section 9.2.7).

[redacted]

10.5.1 Planned Treatment Regimen

10.5.1.1 NLF Treatment Region

Radiesse will be injected into one NLF and Restylane will be injected into the contralateral NLF for the correction of moderate to severe NLFs. Figure 1 illustrates the NLF treatment region.

Radiesse and Restylane are to be injected in the NLF from the alar-tragus line to the oral commissure. [redacted]

In this protocol, laterality for device injection refers to the subject's right or left NLF.

10.5.1.2 Treatment Administration Procedure

At baseline, all subjects will be randomized and will receive injections in the left NLF with Radiesse and the right NLF with Restylane or vice versa. In this protocol, laterality for injection of trial devices refers to the subject's right or left NLF. The investigator must discuss the potential risks of soft tissue injection with the patient prior to treatment, and make sure that the patient is aware of the signs and symptoms of potential complications. Before the treatment, the patient's suitability for the treatment and the need for pain relief should be assessed.

Each NLF of each subject will be treated

reating investigators will be trained on the WSRS and instructed that when treating subjects, the minimal result to be achieved per NLF is at least 1-point improvement on the WSRS from baseline (i.e., optimal correction).

[redacted] If a touch-up is performed, the same randomized product assigned for the initial injection must be used for touch-up injection. A touch-up treatment will only be administered if there are no medical contraindications or existing AEs of concern, as determined by the treating investigator. [redacted]

10.5.1.2.1 Radiesse Administration Procedure

10.5.1.2.1.1 Preparation of the Syringe

[redacted]

1. Prepare the syringes of Radiesse injectable implant and the injection needles before the percutaneous injection, as described below. Only needles provided with the clinical trial material are allowed under this CTP.
2. 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.
3. Peel or twist apart the needle packaging to expose the hub.
4. Remove the Luer-syringe cap from the distal end of the syringe prior to attaching the needle.

[redacted]

5. 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.

[redacted]

6. The needle must be tightened securely to the syringe. Pull off the needle guard to expose the needle.

[redacted]

7. Prime the needle 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.

10.5.1.2.1.2 Preparation of the Injection Region

Any makeup and/or other topical cosmetics in the NLF and cheek area must be removed. As with all percutaneous procedures, Radiesse injection carries a risk of infection and should be conducted with aseptic technique. Any medications used before or after injection must be recorded in the eCRF. [redacted]

Injection Technique

1. According to the subject's randomization assignment (e.g., Radiesse in the left or the right NLF), the product is to be injected into the subdermal tissue [redacted]. The injection technique (e.g., angle and orientation of the bevel, depth of injection, and quantity administered) may vary. Linear threading (also referred to as "tunneling"), serial puncture, or a combination of these injection techniques can be used to achieve optimal results. Every effort should be made to use the same technique(s) in both NLFs. Care must be used to avoid intravascular injection, regardless of technique used.
2. The number of NLF injection locations and volume of filler injected [redacted] are at the discretion of the

treating investigator [redacted].

[redacted]

10.5.1.2.1.3 After-Injection Procedures

When the injection is complete, the treatment site may be gently massaged, if necessary.

[redacted]

Subjects may have mild to moderate injection-site reactions, which typically resolve in < 7 days.

Use the device once and discard in accordance with local safety standards.

10.5.1.2.2 Restylane Administration Procedure

10.5.1.2.2.1 Preparation of Syringe

[redacted]

For safe use of Restylane, it is important that the needle is properly assembled to the syringe. Improper assembly may result in separation of the needle and syringe during injection. Only needles provided with the clinical trial material are allowed under this CTP.

- Grasp the narrow part of the needle shield loosely. Turn the needle shield clockwise until counter pressure is felt.
- Grasp the wider part of the needle shield firmly. Press and turn the needle shield 90° (a quarter turn). The quarter turn is necessary to lock the needle onto the syringe.
- Remove the needle shield.
- Before injecting, press the syringe plunger carefully until a small droplet is visible at the tip of the needle.
- To avoid breakage, do not attempt to bend the needle before or during treatment.

10.5.1.2.2.2 Preparation of the Injection Region

Any makeup and/or other topical cosmetics in the NLF and cheek area must be removed. As with all percutaneous procedures, Restylane injection carries a risk of infection and should be conducted with aseptic technique. Injection procedures can lead to reactivation of latent or subclinical herpes viral infections. Any medications used before or after injection must be recorded in the eCRF. Injection of local anesthesia is <u>not</u> allowed under this CTP.

10.5.1.2.2.3 Injection Technique

1. According to the subject's randomization assignment (e.g., Restylane in the left or the right NLF) [redacted] The injection technique (e.g., needle angle, depth of injection, and quantity administered) may vary. Linear threading, serial puncture, or a combination of these injection techniques can be used to achieve optimal results. Every effort should be made to use the same technique(s) in both NLFs. [redacted] If the overlying skin turns a whitish color (blanching), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Care must be used to avoid intravascular injection, regardless of technique used.
2. The number of NLF injection locations and volume of filler injected [redacted] are at the discretion of the treating investigator, until optimal results are achieved. Augment to optimal 1:1 correction. Do not overcorrect.
3. Aspiration prior to injection is recommended to verify that the needle is not intravascular.
4. Inject Restylane slowly while pulling the needle backward. Injection should stop just before the needle is pulled out from the skin to prevent material from leaking out from the injection site.

5. Do not apply excessive pressure to the syringe at any time. If resistance is encountered the needle should be partially withdrawn and repositioned or fully withdrawn and checked for function.
6. The correction site should be massaged to conform to the contour of the surrounding tissues.
7. If the product is injected too superficially this may result in visible lumps and / or bluish discoloration.

10.5.1.2.2.4 After-Injection Procedures

When the injection is complete, the treatment site may be gently massaged, if necessary.

[redacted]

Subjects may have mild to moderate injection-site reactions, which typically resolve in < 7 days.

Use the device once and discard in accordance with local safety standards.

[redacted]

[redacted]

10.5.2 Selection and Timing of Treatment for Each Subject

Subjects will have an initial injection at baseline (V2) on Day 1, as well as the option for a touch-up injection in one or both NLFs at Week 4 (V3). If a touch-up is performed, the same randomized product assigned for the initial injection must be used for touch-up injection. A touch-up treatment will only be administered if there are no medical contraindications or existing AEs of concern, as determined by the treating investigator.

[redacted]

10.5.3 Treatment Interruption and Modification

In the current trial design, treatment interruption or modification is not expected.

However, if immediate blanching occurs in the treatment area, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society of Dermatologic Surgery guideline [18].

The treating investigator should immediately stop the injection if a trial subject exhibits any of the following symptoms: changes in vision, signs of stroke, blanching of the skin, difficulty walking, or atypical pain during or shortly after the procedure. Subjects should receive prompt medical attention and possibly evaluation by an appropriate healthcare practitioner (specialist) should an intravascular injection occur.

The treating investigator must inform all subjects that, at any time over the trial interval, if the subject experiences any new or unusual symptoms, including signs related to a possible vascular event, including any atypical pain, changes in vision, irregularities in skin color and/or skin texture [redacted], or scabby/crusty skin, the subject must seek immediate medical attention and notify the treating investigator immediately. The treating investigator must refer the subject to a specialist if additional medical attention is deemed necessary.

10.6 Prior and Concomitant Therapy

Medical history and concomitant therapy that is deemed relevant for study conduct by the investigator (e.g., chronic diseases, previous aesthetic treatments) should be documented

in the eCRF. Restrictions regarding concomitant therapy are discussed in detail in Section 9.2.2 (Exclusion Criteria) [redacted].

10.7 Trial Supplies and Packaging of Treatment Supplies

Radiesse and Restylane will be provided by the sponsor. The sponsor will package trial materials according to applicable regulatory requirements. The sponsor will provide all pertinent labeling information, as well as a description of the specific device-packaging conditions.

Radiesse and Restylane are to be used exclusively for treatment of subjects enrolled in this trial and will be labeled as follows: "CAUTION – Investigational Device. Limited to Investigational Use Only." Device labels will also note the manufacturer name and address and the quantity within the package. The IFUs for the respective products will be provided to the investigative sites. Clinical trial supply should be stored in a controlled area with limited access and stored separately from any commercial supplies.

Parts of the trial devices may be subject to reduced labeling according to the applicable regulations. Records about production date, serial number (as applicable), test record related to product quality and stability, and records of transportation, maintenance, and delivery must be kept with the trial devices.

[redacted]

10.8 Receipt, Storage, Dispensing, and Return/Disposal

Upon receipt, trial personnel will verify the contents of all supplies received and promptly notify the appropriate contacts of any discrepancies or damages. Only authorized trial personnel may supply, dispense, and/or administer trial treatment, and only subjects randomized in the trial may receive trial treatment. The investigator is responsible for ensuring an accurate record of inventory is maintained. The investigator or designee will keep a current record of the trial-device delivery to the trial site, inventory, and dispensing, and this record will be made available to the sponsor upon request. Sites will be queried about any discrepancies.

All trial devices must be stored in a secure, environmentally controlled, monitored area with limited access and stored separately from any commercial supplies. [redacted]

Any used needles should be discarded per the appropriate handling and disposal procedures at the site. Any unused and/or partially used trial devices should be retained so the monitor can perform device-accountability procedures.

At the end of the trial and after verification of device accountability, it is the investigator's responsibility to return all unused and/or partially used trial devices and supplies to the sponsor or delegated party. Appropriate records of return must be maintained for accountability purposes. A third-party vendor will destroy the trial devices after completion of the clinical trial report (Section 14.6). Destruction of trial devices at the investigative site may be possible if written authorization is provided by the sponsor. If destruction at the investigative site is agreed upon, a certificate of destruction must be given to the sponsor. All information concerning the date of recycling and disposal upon trial and other aspects (if applicable) must be recorded.

All device-accountability procedures must be completed before the trial is considered complete.

10.9 Device Accountability Procedures

Accountability for trial supplies at the trial site is the responsibility of the investigator.

Access to the trial devices will be controlled, and the trial devices will be used only in the clinical investigation and according to the CTP. The sponsor will keep records to document the physical location of all trial devices from shipment to the investigative sites until return. The investigator or an authorized designee is responsible for ensuring accurate records of receipt, use, and return of the trial devices, are maintained and include:

- The date of receipt and quantity of units received.
- Identification of each trial device (batch number/serial number or unique code).
- The expiry date (if applicable).

- The names of all persons who received, used, or dispensed each device.
- The date or dates of use and time.
- Subject identification.
- Date of return of unused, expired, or malfunctioning trial devices (if applicable).
- All unused or partially used trial devices must be returned to the sponsor or designee immediately after the trial is completed (Section 10.8). Products accidentally destroyed during shipment or at an investigative site should be accounted for and documented. All clinical supplies must be accounted for at the termination of the trial and a written explanation provided for discrepancies.

10.10 Treatment Compliance

[redacted] Variations from the defined trial-treatment administration will be reported as protocol deviations.

10.11 Duration of Trial

Subjects will have a screening period up to 10 days and participate for a maximum duration of 48 weeks (± 7 days) after last injection.

11 TRIAL PROCEDURES

11.1 Visit Schedule

The investigation activities and visit schedule are detailed in the Schedule of Events (Appendix 16.1) and the Trial Design figure (Appendix 16.2).

The screening visit (V1) is required to determine subject eligibility for trial participation; this visit must be completed no more than 10 days prior to baseline (V2) or on the same day of the baseline visit (i.e., baseline and screening can occur on the same day if all screening procedures, [redacted] and laboratory results, have been obtained prior to trial device injection).

The baseline visit (V2) is the day of subject randomization and first administration of the investigational and comparator products. A touch-up injection may be administered (Visit 3, Week 4) to ensure the subject achieves optimal aesthetic correction (Section 10.2). All treatments will be administered at the investigative site [redacted], occurring only after completion of all required pre-injection procedures and assessments.

[redacted]

The primary endpoint visit (PEV) will occur at Week 24 (± 7 days) after last injection, and the EOT visit will occur at Week 48 (± 7 days) after last injection. In the case of a subject's premature discontinuation of the trial, a final assessment (EOT visit) should be performed.

11.1.1 Scheduled Visits

All scheduled visits and applicable trial assessments must occur as noted in Section 11.1 [redacted].

11.1.2 Unscheduled Visits

To ensure subject safety, any subject who, for any reason, requires additional follow-up that does not coincide with a scheduled trial visit should have that visit recorded as an unscheduled visit, during which concomitant medication/procedures and AEs must be assessed and recorded.

[redacted]

11.2 Trial Assessments and Definitions

11.2.1 Effectiveness Assessments

The effectiveness of Radiesse for the correction of NLFs will be evaluated using several assessments. Refer to the respective endpoints (Section 7.2) [redacted] for additional information on the methods and timing of effectiveness assessments.

11.2.1.1 Wrinkle Severity Rating Scale (WSRS)

The WSRS [19] will be used to measure device effectiveness [redacted]. The WSRS is an outcome measure with a 5-point ordinal rating scale for the assessment of NLF severit [redacted].

The WSRS will be used to assess the severity of the NLFs [redacted]

[redacted]

[redacted]

[redacted]

11.2.1.3 Treating Investigator Global Aesthetic Improvement Scale (iGAIS)

Treating investigators will rate each NLF for global aesthetic improvement [redacted]. Investigators will rate the current cosmetic result of the respective NLF, according to the GAIS [redacted].

[redacted]

11.2.1.4 Subject Global Aesthetic Improvement Scale (sGAIS)

Subjects will rate the current cosmetic result of each respective NL [redacted]. At Week 24 after last injection, if a subject responds "no change", "worse", "much worse", or "very much worse" via sGAIS assessment, the subject will be asked for additional explanation as to why the subject rated the NLF as no change or a level of worsening.

[redacted]

11.2.2 Safety Assessments

Standard safety assessments, including documentation of AEs and SAEs reported by the investigator throughout the trial, will be evaluated.

Refer to the respective endpoints (Section 7.2.2) [redacted] for additional information on the safety assessments.

11.2.2.1 Adverse Events (AEs) / Serious Adverse Events (SAEs)

All AEs/SAEs reported by trial subjects, investigators, or other trial staff after the time of informed consent through the last trial follow-up visit will be recorded. All AEs/SAEs will be recorded regardless of causality.

Additional information (e.g., definitions, reporting requirements) is provided in Section 12. All AEs/SAEs will be assessed throughout the trial, including on-site trial visits and during follow-up phone calls.

Any AE/SAE must be documented in the subject's file and on the AE eCRF page.

Any AE/SAE observed will be fully investigated, documented, and followed until the AE/SAE is either resolved or adequately explained, until the EOT visit (Section 12.2.2).

Serious AEs occurring after the end of the observational period only need to be reported if the investigator considers the SAE to be related to the trial devices. These reports generally will not be entered into the investigation database.

[redacted]

[redacted]

[redacted]

11.2.3 Additional Data Collected

Other data collected are as follows:

- Demographics and other baseline characteristics, including height and weight;

[redacted]

- Injection technique, location, and depth;
- Relevant medical history/concomitant diseases;

- Concomitant therapies; and
- Vital signs.

[redacted]

11.2.3.1 Laboratory Assessments

Non-fasting clinical laboratory tests will be performed at screening (V1) and Week 24 after last injection. These lab tests include clinical chemistry, hematology, and urinalysis to rule out underlying disease that may exclude the subject from participation or require initiation of medical care during the trial [redacted].

[redacted]

[redacted]

11.2.3.2 Vital Signs

Vital signs will be measured on subjects after they have been seated for approximately five minutes. Resting heart rate and blood pressure (systolic and diastolic, preferably on the same arm each time) will be measured at screening (V1) and Week 24 after last injection.

[redacted]

11.2.4 Appropriateness of Assessments

Appropriateness of the selected trial assessments is detailed in the respective Effectiveness Assessments (Section 11.2.1) and Safety Assessments (Section 11.2.2).

12 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

12.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including an abnormal laboratory finding) in subjects, users, or other persons, whether or not related to the Investigational medical device (IMD).

Note:

1. This definition includes events related to the IMD or the comparator.
2. This definition includes events related to the procedures involved.
3. For users or other persons, this definition is restricted to events related to the IMD.

12.1.1 Details of an AE

The period of observation for an AE extends from when the ICF is signed until the subject's last trial visit. Any medical occurrence between the time the ICF is signed and the first treatment with the IMD is an AE and has to be documented in the subject's file and on the AE eCRF page. Any observed AE will be fully investigated, documented, and followed until the event is either resolved or adequately explained, until the EOT visit. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered the AE rather than the procedure itself. New AEs reported to the investigator during the observational period, after the last treatment with the IMD, must be documented, treated, and followed like all other AEs.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset at or after the first administration of trial treatment. If an AE starts prior to treatment but worsens at or after treatment, the investigator records this observation as a new AE with onset = time of worsening.t = time of worsening.

A pre-existing condition noted in the medical history should not be reported as an AE, unless the condition worsens or the disease reoccurs during the reporting period. To determine whether a condition has worsened, it is compared to the subject's condition at screening.

Elective treatments planned before screening, and which are documented in the subject's source data, are usually not regarded as AEs. However, elective procedures should be postponed, if possible, until the subject completes their participation in the trial.

12.1.2 Reporting and Handling of an AE

Data pertaining to AEs will be collecte [redacted]. The investigator will assess and

record any AE in detail in the subject's file and on the AE eCRF. The following information must be recorded:

- AE diagnosis or main symptom;
- AE localization (restricted to treatment area, systemic). If a local reaction, the corresponding area should be reported;
- Date of onset;
- Intensity (maximum observed using the Severity Grading scale; Section 12.1.3);
- Causal relationship (not related, related) to investigational device and study procedure;
- Causal relationship (not related, related) to comparator device;
- Serious (yes, no), date serious since, and reason for seriousness;
- Outcome (Section 12.1.5);
- AE leading to discontinuation of the clinical trial (yes, no);
- Action taken with medical device;
- Action taken related to the AE; and
- Stop date.

In cases of an SAE (defined in Section 12.2), the investigator must also complete an SAE Report Form and report it to the sponsor and CRO immediately as described in Section 12.2.2.

12.1.3 Severity Grading for an AE

The clinical severity (i.e., 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 daily activities.

The investigator is required to grade the severity (i.e., intensity) of each AE.

12.1.4 Causal Relationship of an AE with an Investigational Medical Device

An AE is considered to be "related" to IMD or to the treatment procedure if a causal relationship between the IMD or the treatment procedure and an AE is at least reasonably

possible (i.e., the relationship cannot be ruled out). In this case, the non-serious event is considered an "adverse device effect" (Section 12.3). If the event is serious, it is a "serious adverse device effect" (Section 12.4).

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

12.1.5 Outcome Categories for an AE

Reportable outcomes and/or sequelae of an AE may include the following:

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

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

12.2 Definition of a Serious Adverse Event (SAE)

An SAE is an adverse event that:

a) led to death;

b) 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 including chronic diseases, or

   3) inpatient 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.

c) 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 CTP, without serious deterioration in health, is not considered an SAE.

12.2.1 Details of an SAE

In cases of fatality, the cause of death is considered the AE, and the death is considered its outcome. In this case, the primary cause of death (i.e., 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. In cases of death, an autopsy report should be submitted (if available). The date and cause of death should be recorded.

Planned hospitalization for a pre-existing condition is not considered an SAE. If a subject experiences an additional AE that prolongs a pre-planned hospitalization, this event is considered an SAE and should be reported as such. Hospitalizations for elective treatments planned before screening and which are documented in the subject's source data are usually not regarded as SAEs.

In addition, device deficiencies, as defined in Section 12.5, that might have led to an SAE if:

a) suitable action had not been taken; or

b) intervention had not been made; or

c) if circumstances had been less fortunate

should be categorized as an SAE and reported accordingly.

12.2.2 Reporting and Handling of an SAE

All SAEs that occur during the clinical trial period, whether considered to be related to the IMD or not, must be reported via fax, phone, or e-mail, and an SAE Report Form should be submitted to the sponsor and the CRO immediately upon knowledge of the event. The investigator will report the SAE to the clinical trial management departments of the clinical trial institution and the CRO. Further reporting details will be outlined in the Safety Management Plan.

Although all information required for completion of 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 (unique subject number);
- A suspect product and how the treatment relates to the SAE;
- An identifiable reporting source (investigator/investigative site identification); and/or
- An event or outcome that can be identified as serious.

The investigator must report SAEs to the sponsor and the CRO, as defined in Section 12.2 and in compliance with Chinese GCP (Article 71), and to the site's IEC/IRB, through the medical device clinical trial management department, per their reporting guidelines.

The sponsor's Global Product Safety department will conduct an evaluation of the SAE and report the results of such evaluation to the CRO, who will, on behalf of the sponsor, report to regulatory agencies, IECs/IRBs through the medical device clinical trial management department, and investigators.

The investigator must supply further supporting information, and a detailed SAE description is an integral part of this supporting information. Follow-up SAE reports should be sent without delay to the sponsor and the CRO as an SAE Report Form (marked as a "follow-up" report), and the eCRF has to be updated accordingly to avoid discrepancies. The SAE has to be followed until the SAE is resolved/recovered or a plausible explanation is available. The SAE will be followed-up only in the Global Product Safety database after final SAE reconciliation is completed.

An SAE occurring after the end of the observational period would need to be reported if the investigator considers the event to be related to IMD. These reports generally will not be entered into the investigation database. Following database close for the trial, any ongoing SAEs will be followed until resolution or stabilization under the responsibility of the investigator per standard of care.

The investigator should complete and send any SAE Report Forms (including any follow-up forms) to the following contacts:

MERZ	CRO
Merz Pharmaceuticals GmbH Global Product Safety Department – Merz Aesthetics Eckenheimer Landstrasse 100 D – 60318 Frankfurt/Main [redacted]	[redacted]

12.3 Definition of an Adverse Device Effect (ADE)

An ADE is defined as an adverse event related to the use of an IMD.

Note:

1. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the IMD.

2. This definition includes any event resulting from use error or from intentional misuse of the IMD.

12.4 Definition of a Serious Adverse Device Effect (SADE)

An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE (Section 12.2).

12.4.1 Definition of an Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is a serious adverse device effect which, by its nature, incidence, severity, or outcome, has been identified in the current version of the risk-analysis report.

12.4.2 Definition of an Unanticipated Serious Adverse Device Effect (USADE)

A USADE is defined as follows:

- Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), risk-analysis report, or IFU.
- Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

12.5 Reporting of Pregnancy

Any pregnancy that starts during the clinical trial must be reported by the investigator to the sponsor and CRO immediately. Pregnancies and pregnancy follow-up should be reported on a Pregnancy 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 IMD. In addition, each pregnancy has to be reported on the AE eCRF page (i.e., as a non-serious AE due to device exposure before or during pregnancy). Pregnancy Forms (including any follow-up forms) should be submitted to the contacts referenced in Section 12.2.2.

If a subject becomes pregnant during the trial, the subject must not receive further treatments (i.e., touch-up treatment); however, the subject will remain in the trial. In cases of pregnancy, clinical laboratory tests will not be performed.

12.7 Definition of Device Deficiency

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or effectiveness.

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

12.7.1 Reporting and Handling of Device Deficiencies

All device deficiencies shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor.

The investigator should retain the device and/or needle in question for future inspection and investigation by the sponsor, if necessary.

The investigator will attempt to evaluate if the deficiency might have led to an AE if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate. A device deficiency that could have led to a SADE (Section 12.4) is to be reported in the same way as an SAE.

For reporting of device deficiencies:

- A Device Deficiency eCRF page must be completed and submitted by the investigator, irrespective of the seriousness of the case.

- A Device Deficiency eCRF page must be completed and submitted by the investigator, irrespective of whether the complaint led to an AE.
- If a device deficiency is associated with an SAE, the investigator must also complete and submit an SAE Report Form (Section 12.2.2) in addition to the Device Deficiency eCRF page.

If a device deficiency is not related to a specific subject (e.g., damaged packaging occurring prior to the subject's visit), the investigator should complete a paper Device Deficiency Form, instead of the eCRF page, and send immediately to the following contacts:

MERZ	CRO
Global Quality – Complaint Management [redacted] Merz Pharma & Co. KGaA Global Quality Eckenheimer Landstrasse 100 D – 60318 Frankfurt/Main [redacted]	[redacted]

The sponsor's Global Quality department will decide if the device and/or needle needs to be returned and to whom the device and/or needle should be sent for investigation.

13 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of trial planning. Further details on the statistical and analytical aspects will be presented in the statistical analysis plan (SAP) that will be prepared and completed prior to database close.

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 unblinding, respectively, will be described in amendments to the CTP and/or the SAP. All deviations and/or alterations will also be summarized in the clinical trial report.

13.1 Estimation of Sample Size

The sample size was calculated separately for safety and for the primary effectiveness endpoint as follows:

13.1.1 Safety

The safety aim of the trial is to generate a database with short-term and sufficient long-term safety data. Based on the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E1 guideline, 100 subjects treated and observed over 48 weeks is deemed sufficient. [redacted]

[redacted]

13.1.2 Effectiveness

The sample size considerations for the primary effectiveness endpoint (i.e., change from baseline to Week 24 after last injection on the WSRS [redacted] are based on the following:

- Type I error, $\alpha = 0.05$ (two-sided) and
- Non-inferiority margin of 0.5.

[redacted]

When using the 118 subjects randomized for safety and applying a drop-out rate of 15% from randomization to the Per Protocol Set (PPS), [redacted], 100 subjects would be available for analysis of the primary effectiveness endpoint on PPS.

For analysis on the Full Analysis Set (FAS) even more subjects are expected. [redacted]

To ensure a reasonable number of subjects is enrolled per investigative site, the number of subjects treated at each site should not exceed 20 in case of seven recruiting sites, 24 in case of six recruiting sites, and 28 in case of five recruiting sites.

13.2 Randomization

Each subject screened will be given a screening number. Only the subjects who are randomized will receive a randomization number at baseline (V2) through an electronic system. All eligible subjects will be randomized 1:1 to one of the following groups:

- Group 1: left NLF: Radiesse, right NLF: Restylane or
- Group 2: left NLF: Restylane, right NLF: Radiesse.

Randomization will be stratified by investigative site and performed in blocks. All randomization codes will be generated by an electronic system. The system will allocate the subject's randomization number and will determine the subject's group assignment (Group 1 or Group 2) to be used at each injection visit. The randomization number for each subject will then be recorded in the eCRF.

13.3 Populations for Analysis

The following analysis sets will be defined:

- The randomized set is defined as all subjects randomized into the trial.
- The Safety Evaluation Set (SES) is defined as all subjects who are randomized and receive investigational product at least once.
- The FAS is defined as all subjects who are randomized, receive investigational product, and have at least one after-baseline effectiveness assessment.
- The PPS is the subset of subjects in the FAS who have no major protocol deviations or other events that impact analysis of the primary effectiveness endpoint. Final determination of which events lead to exclusion from PPS will be made prior to database close.

13.4 Analysis of Trial Data

Effectiveness and safety endpoints are provided in Section 7.2.1 and Section 7.2.2 respectively.

All statistical analyses will be performed using Statistical Analysis System (SAS) statistical analysis software [redacted].

All safety analyses will use the SES. Effectiveness analyses will be performed on the PPS and for sensitivity on the FAS.

13.4.1 Effectiveness Analyses

There will be one confirmatory analysis of the primary effectiveness endpoint. All other analyses are supportive.

13.4.1.1 Primary Effectiveness Endpoint

If the expected mean intra-individual difference between Radiesse and Restylane in WSRS change from baseline to Week 24 is denoted by δ, the null and alternative hypotheses to be tested are:

$$H_0 : \delta \geq 0.5 \text{ (null hypothesis)} \text{ versus } H_1 : \delta < 0.5 \text{ (alternative hypothesis)}$$

with 0.5 being the non-inferiority margin. To test the null hypothesis, a two-sided 95% CI will be constructed around δ. H0 will be rejected if the upper bound of the two-sided 95% CI lies below the non-inferiority margin of 0.5. It will then be concluded that Radiesse is non-inferior to Restylane and is effective. The two-sided 95% CI for δ will be constructed by applying a repeated-measures analysis of covariance (ANCOVA) model to the WSRS change from baseline to Week 24. This model will include treatment (i.e., Radiesse or Restylane), investigative site, touch-up performed (i.e., yes/no), and randomized sequence (i.e., "left NLF treated with Radiesse and right NLF treated with Restylane" or "left NLF treated with Restylane and right NLF treated with Radiesse") as fixed class effects and baseline WSRS [redacted] as a fixed covariate. That observations are dependent over treatment (due to the split-face design) will be modelled using treatment as a repeated factor. The SAS procedure "proc mixed" will be used with the covariance matrix for treatments left "unspecified". The latter allows estimation of different variances for the two treatments.

The least squares means (lsmeans) statement will be used to derive a point estimate as well as a 95% CI for δ.

The confirmatory analysis will be based on the PPS. [redacted] he variables (VAR) statement will include the variables treatment, investigative site,

randomized sequence, age, sex, touch-up, and WSRS at visits before Week 24. [redacted]

[redacted]

13.4.1.2 Secondary Effectiveness Endpoints

For both GAIS scores, the proportion of subjects with any improvement at Week 24 will be calculated by treatment and given as number of subjects with improvement/number of subjects in the corresponding analysis (n/N) and as percentage (%). In addition, the difference of the two treatment response proportions will be stated. Cross tables will be provided showing number (and percentage) of subjects with any (or no) GAIS improvement of the Radiesse-treated side versus any (or no) GAIS improvement of the Restylane-treated side.

[redacted]

13.4.2 Safety Analyses

All safety endpoints will be analyzed for the SES.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version that is in effect at the time the database is closed.

Only TEAEs will be analyzed, which are defined as AEs with onset at or after the first administration of Radiesse or Restylane. If an AE starts prior to treatment but worsens at or after treatment, the investigator records this observation as a new AE with onset = time of worsening. new AE with onset = time of worsening.

Similarly, only those device deficiencies that are reported to be associated with devices that were used to treat subjects will be analyzed.

Non-TEAEs and device deficiencies reported for devices not used for treatment but documented in the eCRF will be listed only.

For public disclosure, incidences of non-serious TEAEs regardless of relationship will be calculated at the system organ class (SOC) level and at the preferred term (PT) level and will be presented by treatment (where applicable) and overall.

In case of a missing causal relationship of an AE, the worst-case principle will be applied (i.e., a missing causal relationship will be set to “related”).

13.4.2.1 Secondary Safety Endpoints

Incidences of TEAEs related to Radiesse will be calculated at the SOC level and at the PT level and will be presented by treatment (where applicable) and overall.

[redacted]

[redacted]

13.5 Special Statistical/Analytical Issues

[redacted]

13.5.2 Multiple Comparisons/Multiplicity

No multiplicity adjustments are required. Only one confirmatory analysis of the primary effectiveness endpoint will be performed. All other analyses are for exploratory or sensitivity purposes.

[redacted]

14 ADMINISTRATIVE PROCEDURES

14.1 Trial Monitoring

Trial monitoring will conform to all applicable regulatory standards and guidelines.

The sponsor or designee will monitor the trial through periodic site visits to verify:

- Data authenticity, accuracy, and completeness.
- Protection of subject rights and safety.
- Conduct of the trial is in accordance with the currently approved protocol and all applicatory regulatory and IEC/IRB requirements and guidelines.

Investigators agree to grant access to all relevant documents and provide support at all times for trial-monitoring activities. These activities will be performed in a manner that ensures maintenance of subject confidentiality (Section 5.3 and Section 5.4). Further details of monitoring activities will be provided in the monitoring manual.

14.2 Data Quality Assurance and Standardization Procedures

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

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, evaluations, and validation methods). [redacted]

This trial will be monitored regularly by a qualified monitor from the CRO according to EN ISO 14155, Chinese GCP, Chinese regulatory authority requirements, and the respective standard operating procedures [redacted].

14.3 Source Documentation Requirements

All data collected from a subject during the course of a clinical investigation should be retained in the respective source documentation (e.g., subject file). Although not an exhaustive list, this information should include a descriptive statement on the informed consent procedure (Section 5.2). The investigator must also confirm by written statement in the source documentation that all inclusion criteria and all exclusion criteria were checked prior to inclusion of the subject. In addition to this statement, the subject's meeting or non-meeting of the in- and exclusion criteria and eligibility criteria must be traceable in the source documentation. The childbearing potential of female subjects must be

documented in the file. The site will keep a source-data location list, which will outline for the different data categories, including electronic data (e.g., demographics, relevant medical history, and AEs, etc.), which document serves as its source [redacted].

Further information (e.g., procedures for verification, validation, and securing of applicable electronic clinical data systems) will be described in the data management plan.

14.3.1 Data Management

Data required according to this protocol are to be recorded in the web-based eCRFs (EDC system). All users who have access to the EDC system will be trained for their respective roles, and their training will be documented. After successful completion of the training, participants will receive a training certificate, which will be a pre-requisite for access to the eCRF. Access to the eCRF will be password controlled.

Data-plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the EDC system; answers to queries or changes to the data will also be documented in this system directly by an authorized member of the investigator's trial personnel. The audit trail in the EDC system will document all changes. Edit checks generate automatic queries during data entry when a field is not populated according to specifications defined in the data validation plan. Manual queries to be answered by trial personnel can be raised during source data verification and/or during medical, safety, and/or data management review. After all data are entered and all queries are solved, the database will be closed and unblinding will take place. If any data changes are required after database close, these changes will be documented according to the respective SOP.

[redacted]

14.3.2 Data Review and Clarification Procedures

By electronically signing the eCRF with an automated time stamp, the investigator will confirm that all investigations have been completed and conducted in compliance with the CTP and that reliable and complete data have been entered into the eCRF.

All data required by this CTP are to be recorded in the eCRF as soon as possible. However, direct entries are not allowed; data must be transcribed from the source documentation (e.g., subject file, scales) to the eCRF.

If eCRF corrections are necessary, an authorized member of the investigator's trial personnel will enter the correct data into the web-based eCRF. The audit trail in the EDC system documents all changes.

The CRO's and sponsor's data-management functions will be responsible for data processing, in accordance with the CRO's and sponsor's data-management procedures. Database close will occur only after quality-assurance procedures have been completed.

Entries from questionnaires completed by the subject will be entered into the eCRF by trial personnel. If corrections in the questionnaires 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. Per Chinese GCP, clinical trial records, as the original materials, must not be changed without authorization. If such a change is required, the reason shall be explained, and the explanation shall be signed and dated.

14.3.3 Direct Access to Source Data/Documents

As stated in Section 14.1, investigators agree to grant access to all relevant documents and to provide support for monitoring activities.

Subjects providing informed consent (Section 5.2) agree to allow the sponsor or designee access and copying rights to pertinent information in their medical records concerning their participation in this trial. The investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the subjects in this trial. This information may be shared with regulatory agencies; however, the sponsor undertakes not to otherwise release the subject' s personal and/or private information.

14.3.4 Auditing

Audits shall be conducted by qualified auditors to evaluate compliance with the CTP, sponsor's current written procedures, and any applicable regulatory requirements. These audits may cover all involved parties, systems, and facilities and are independent of, and separate from, routine monitoring or quality-control functions.

An audit can be conducted:

- as a routine part of the sponsor's quality-assurance program;
- to assess the conduct of the monitoring activity;
- whenever there are serious or repeated CTP deviations or suspicion of fraud;

- to bring an investigative site into "inspection readiness" (i.e., to prepare the investigative site for a potential regulatory inspection), and/or
- when requested or suggested by a regulatory authority.

Audit results shall be documented and communicated to relevant parties, if applicable.

14.4 Protocol Deviations and Amendments

14.4.1 Protocol Deviations

Investigators will not deviate from or alter the CTP without written agreement between the principal investigator and the sponsor and written approval by the IEC/IRB based on prior review. Exceptionally, in case of urgent clinical need (e.g., to minimize emergent risk to a subject), the principal investigator may deviate from the protocol without this written agreement. After mitigating the immediate risk, the investigator must contact the sponsor and the CRO without delay to report the incident.

In the event that an investigator does not comply with the Clinical Trial Agreement or the CTP, the sponsor will be notified of the site's noncompliance.

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

- Visiting the investigator;
- Telephoning the investigator; and/or
- Corresponding with the investigator.

Repeated noncompliance with the signed Clinical Trial Agreement, the CTP, or any other conditions of the trial may result in further escalation in accordance with the sponsor's written procedures, including securing compliance or, at its sole discretion, the sponsor may terminate the investigator's participation in the trial.

If CTP deviations occur at the investigation site, these will be detected during routine monitoring visits and reported in the visit report. In addition, a list containing all deviations reported from monitoring visits will be maintained by the CRO, analyzed for frequency and severity, and discussed with the sponsor on a regular basis. Depending on the type of deviation, corrective and preventive actions will be defined and implemented accordingly.

14.4.2 Protocol Amendments

Approved CTP amendments will be provided to investigators by the sponsor. The principal investigator is responsible for notifying the IRB/IEC of the CTP amendment (if administrative changes) or obtaining IRB/IEC's approval of the CTP amendment (if changes in subject care or safety), according to instructions provided by the sponsor.

Acknowledgement/approval by the IRB/IEC must be documented in writing prior to implementation of the CTP amendment. Copies of this documentation must also be provided to the sponsor.

14.5 Record Retention

Essential documents should be retained per applicable regulations and as instructed by the sponsor. Essential documents at the investigative site include, but are not limited to:

- Source documentation (e.g., subject files);
- Subject identification code list (i.e., provided by template to the investigator, along with the Investigator Site File, at the beginning of the investigation), which identifies the subject by number, name, and date of birth;
- A copy of the CTP and any amendments;
- A CD/DVD with eCRF data and any associated subject-related source data (or, where applicable, authorized copies of source data);
- Signed ICFs;
- Copies of site investigators' and co-workers' curricula vitae;
- Copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies);
- Copies of all relevant correspondence between the investigator and the monitor and between the investigator and the sponsor;

[redacted]

- Copies of investigational device disposition records;
- Copies of safety information reported during the investigation and submitted by the sponsor.

Trial documents may not be destroyed by site personnel prior to the end of the required retention period, as specified by local regulations. The investigator or the institution must inform the sponsor in due time if the investigator leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

Upon closure of the trial, the investigator must maintain all trial-site records in a safe and secure location. The investigator is responsible for the integrity, retention, and security of all trial-related records. The investigator must ensure that any reproductions of the original records are legible and provide a true and accurate copy of the original. Accurate, complete, and current records must be stored in a manner to permit easy and timely retrieval for the sponsor or any applicable regulatory authorities.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements, with the minimum retention time being the longest of those times dictated by institutional requirements, local laws or regulations,

or the sponsor's standard procedures. The investigator must notify the sponsor in the event of any changes to archival arrangements due to withdrawal of the investigator's responsibility for keeping trial records to ensure that suitable arrangements for the retention of trial records are made.

14.6 Clinical Trial Report

A clinical trial report containing effectiveness and safety analyses will be generated after all subjects have completed the trial. The content of the report will meet China CMDE requirements.

14.7 Publication of Trial Results

The results of this trial and any discoveries related to this trial, regardless of whether they have technical or medical character, are the property of the sponsor.

The CTP, trial data, and information related to the trial or the sponsor's products or research programs are to be kept confidential and may not be disclosed without the consent of the sponsor.

The investigator agrees that the results of this trial may be used for submission to national or international registration and supervising authorities. Upon completion of the trial, publication or disclosure of trial results is to follow the terms contained in the sponsor's publication policy.

The sponsor will ensure the clinical trial is registered, and results are reported in public registries, at minimum in case one or both is required by law and/or other applicable requirements (e.g., on ClinicalTrials.gov if required by U.S law and/or on Chinese Clinical Trial registry (ChiCTR)). Trial registration may include a list of investigative sites, as applicable.

14.8 Financial Disclosure

Financial aspects of the investigation will be documented in an agreement between the sponsor, the CRO, and each investigator or any other involved party, and must be confirmed in writing before the investigation commences.

14.9 Investigator Compliance

The investigator will conduct the trial in compliance with the CTP, EN ISO 14155, Chinese GCP, the Declaration of Helsinki, and Chinese regulatory authority requirements.

Additional information is reported in Section 14.4.1.

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16 APPENDICES