1 TITLE PAGE

Prospective, multicenter, controlled, evaluator-blind, randomized study to investigate the effectiveness and safety of diluted RADIESSE® for treatment of décolleté wrinkles

Study Identifier:	M930521003 / NCT05163353
Version Date:	10-MAR-2022, Version 5.0 26-OCT-2021 Version 4.0 02-SEP-2021 Version 3.0 29-JUL-2021 Version 2.0 04-AUG-2020 Version 1.0
Investigational Medical Device:	RADIESSE®
Study Design:	Prospective, multicenter, randomized, evaluator-blinded, parallel-group study
Sponsor:	Merz North America, Inc. See additional information in CCI [redacted]

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

Changes to Previous Versions of this Protocol

Version and Date	Key Changes
Version 5.0, 10-MAR-2022	CCI [redacted]
Version 4.0, 26-OCT-2021	A list of adverse events (AEs) of interest was added. Any AE of visual disturbance and other events of interest will be reported to the sponsor and to FDA. CCI [redacted] The process for suspension or termination of the trial was further defined.
Version 3.0, 02-SEPT-2021	The indication statement was removed from the title page and the synopsis.
Version 2.0, 29-JUL-2021	CCI [redacted] The sample size has been increased and the randomization ratio has been revised to expand the safety data available. CCI CCI [redacted] The Global Aesthetic Improvement Scale (GAIS) assessments by the subject and investigator at Week 24 have been upgraded to serve as additional secondary effectiveness endpoints. The protocol has been modified to ensure that subjects with detected abnormalities on visual-function assessments post-treatment will be

	referred to an ophthalmologist for evaluation. CCI [redacted]

2 SYNOPSIS

Title of Study	Prospective, multicenter, controlled, evaluator-blind, randomized study to investigate the effectiveness and safety of diluted RADIESSE® for treatment of décolleté wrinkles.
Study Identifier	M930521003
Investigators, Study Sites	This study will be conducted at up to ten study sites in the United States.
Investigational Medical Device	RADIESSE®
Objectives	*Effectiveness* • Confirm the effectiveness of treatment with diluted Radiesse for correction of moderate to severe décolleté wrinkles by demonstrating superiority versus untreated-control. *Safety* • Demonstrate the safety of repeat treatment with diluted Radiesse for correction of décolleté wrinkles.
Effectiveness Evaluation	*Primary endpoint* • Proportion of responders at Week 24 on Merz Aesthetic Scale (MAS) Décolleté Wrinkles-At Rest as assessed live by a blinded evaluator, where response is defined as at least 1-point improvement from baseline. *Secondary endpoint* • Proportion of responders at Week 24 on MAS Décolleté Wrinkles-Dynamic as assessed live by a blinded evaluator, where response is defined as at least 1-point improvement from baseline. • Proportion of subjects with any improvement, defined as a rating of + 1, + 2 or + 3 on Subject Global Aesthetic Improvement Scale (GAIS) at Week 24. • Proportion of subjects with any improvement, defined as a rating of + 1, + 2 or + 3 on Investigator GAIS at Week 24.
Safety Evaluation	*Secondary endpoint* • Incidence of treatment-emergent adverse events (TEAEs) related to treatment with diluted Radiesse, as reported by the treating investigator throughout the study.
Study Design Overview, and Methodology	This is a prospective, multicenter, randomized, evaluator-blinded, parallel-group study designed to evaluate the effectiveness and safety of diluted Radiesse in healthy adult females desiring correction of moderate to severe décolleté wrinkles. All eligible subjects will be randomized at a 3:1 ratio to treatment with diluted Radiesse (Group A) or to untreated control followed by delayed treatment with diluted Radiesse (Group B).

	Subjects in Group A will receive three treatments in total at Day 1, Week 6, and Week 12. Additionally, subjects in Group A will have the option for one additional retreatment at Week 36. CCI [redacted] Subjects in Group B will receive three treatments upon completion of all effectiveness assessments at Week 24. CCI [redacted] Untreated-control/delayed-treatment subjects will not be offered an additional optional retreatment. Subjects will have a screening period of up to 10 days. All enrolled subjects will participate for a maximum duration of 84 weeks (± 14 days).
Number of Study Subjects	Approximately 152 subjects will be randomized, and 120 evaluable subjects are planned for this study.
Main Inclusion/ Exclusion Criteria	Key inclusion criteria: • Female between ≥ 30 and ≤ 65 years old at the time of the screening. • Subjects seeking improvement of décolleté wrinkles. CCI [redacted] Key exclusion criteria: • Any previous surgery, including plastic surgery or permanent surgical implant in the treatment area. • Previous treatment with collagen fillers, calcium hydroxylapatite, and/or long-lasting hyaluronic acid (HA) fillers in the décolleté within the past 24 months, or with other HA fillers in the décolleté within the past 12 months. • Previous treatment with botulinum toxin, ablative or fractional laser, microdermabrasion, microneedling, chemical peels, and/or non-invasive skin tightening in the décolleté within the past 6 months.

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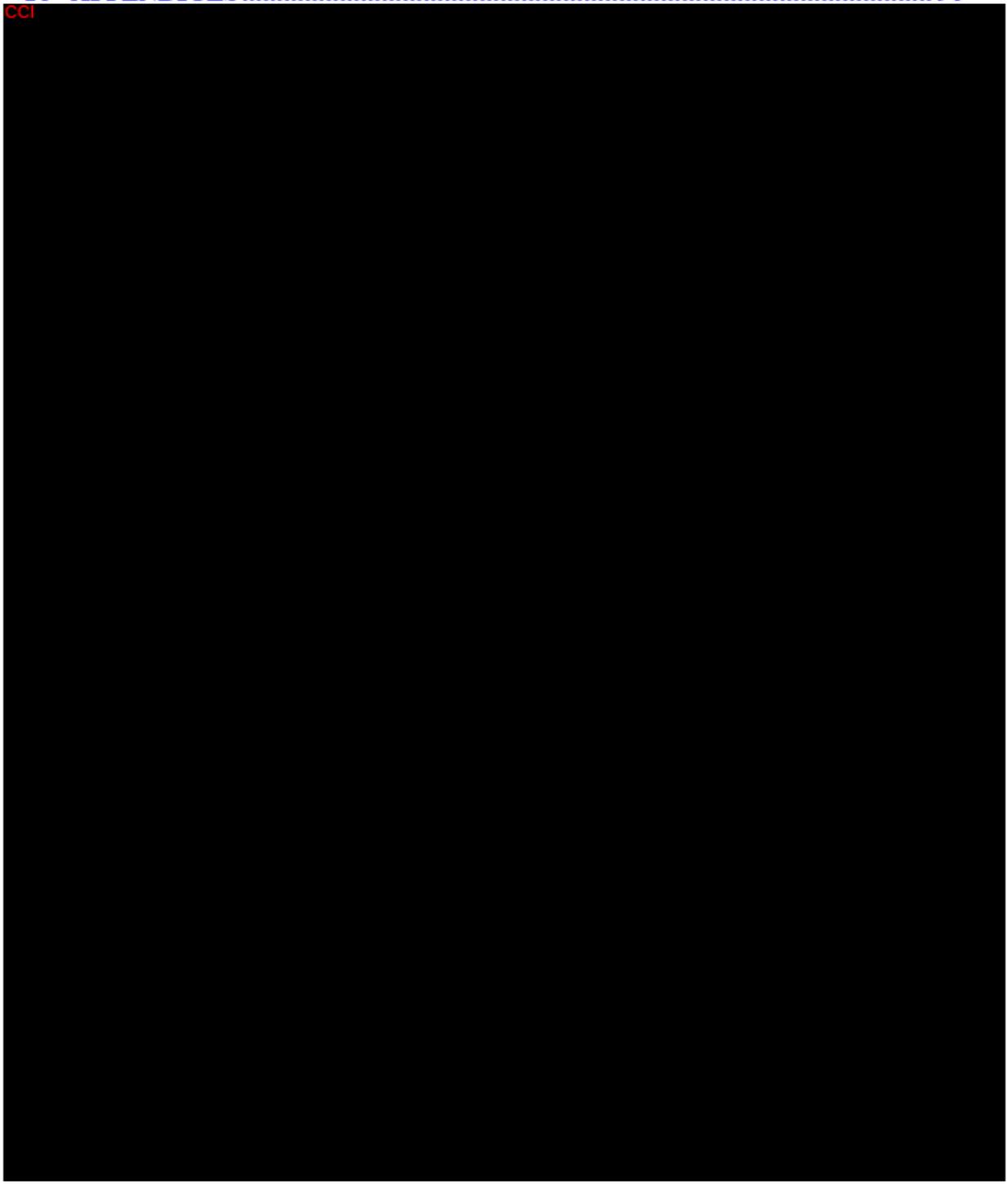

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
CaHA	Calcium hydroxylapatite
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSP	Clinical study protocol
CCI [redacted]	
DRM	Data review meeting
eCRF	Electronic case report form
CCI [redacted]	
EDC	Electronic data capture
EN ISO	International Organization for Standardization (ISO) as adopted by the European Union (EN)
CCI [redacted]	
FCS	Fully conditional specification
FDA	Food and Drug Administration, US
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HA	Hyaluronic acid
HIV	Human immunodeficiency virus
ICC	Intra-class correlation coefficient
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC	Independent ethics committee
IFU	Instructions for use
iGAIS	Investigator Global Aesthetic Improvement Scale
IMD	Investigational medical device
CCI	[redacted]
IRB	Institutional Review Board
CCI	[redacted]
ITT	Intent-to-treat
ITT-OC	ITT observed cases
CCI	[redacted]
MAS	Merz Aesthetic Scale
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation (SAS Procedure)
NSAID	Non-steroidal anti-inflammatory drug
PHI	Protected health information
PPS	Per protocol set
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SES	Safety evaluation set
sGAIS	Subject Global Aesthetic Improvement Scale
SOC	System organ class
SOP	Standard operating procedure
CCI	[redacted]
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
Tx	Treatment

UADE	Unanticipated adverse device effect
UDI	Unique device identifier
US	United States
UV	Ultraviolet

5 ETHICS

5.1 Ethical Conduct of the Study

This study will be performed in accordance with the principles outlined in the Declaration of Helsinki and in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's Good Clinical Practice (ICH-GCP), EN ISO 14155, the Code of Federal Regulations (CFR), and any applicable regional or national laws and regulations. The study will adhere to all applicable subject privacy requirements.

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

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency) procedures that prioritize the reporting of protocol deviations that could impact subject safety will be defined and communicated to the appropriate IEC/IRB. In addition, changes in protocol conduct necessary to promptly ensure subject safety, such as conducting telephone or virtual visits for safety monitoring rather than on-site visits, can be implemented immediately with subsequent communication and review by the appropriate IEC/IRB and notification to regulatory authorities.

5.2 Informed Consent

Verbal and written informed consent must be obtained from every subject prior to the initiation of any screening or study procedures. The investigator will follow a standard process for obtaining consent that complies with all applicable regulatory requirements. If applicable, a certified, local-language translation of the informed consent form (ICF) will be provided.

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

The original and any amended signed and dated ICF(s) must be retained at the study site, and a copy of the signed and dated ICF(s) must be given to the subject.

During the study, the subject will be informed if information becomes available that may be relevant to the subject's willingness to continue participation in the study. Each ICF will

include contact information (with a phone number) the subject should use to communicate any medical concerns 24 hours a day. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), if re-confirming subjects' consent is deemed necessary due to significant changes made to the protocol and/or monitoring plan that could impact subjects, then:

- Alternative ways of obtaining consent will be defined as subjects should not visit sites for the sole purpose of re-confirming consent. For example, subjects will be contacted via phone or video calls and verbal consent will be obtained, supplemented with written confirmation (e.g., via e-mail).
- IEC/IRB approved updated subject information sheets and ICFs will be provided to subjects by e-mail, mail or courier when re-confirming consent.
- All instances of re-confirming consent that are obtained through alternative ways will be documented.

The subjects' consent will be re-confirmed through regular consent procedures at the earliest opportunity once/if the subjects are able to return to the sites, if applicable.

5.3 Subject Privacy

The subject will be informed of procedures to protect subject privacy. Under U.S. federal law (the Privacy Rule) any protected health information (PHI) that is created or obtained during this study cannot be used or disclosed without permission. The currently designated statistical CRO processes subject data 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 the European-focused General Data Protection Regulation law (GDPR). Informed consent on data processing will be obtained in writing directly from the subject before recording of any data. Authorization to use and disclose 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).

At the conclusion of the study, subject photographs will be stored and archived electronically by the sponsor and the study site. Photographs allowing identification of the subject will be published only if the subject has given written permission.

5.4 Confidentiality of Subject Information

Subject pseudo-anonymity is to be maintained during the study. Subjects will be identified by a unique subject number on all study 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 sign an

authorization to 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 study participation. At a subject's request, the subject's medical information may be provided to the subject's personal physician or other appropriate medical personnel.

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

6 INTRODUCTION

6.1 Background

Many factors contribute to the natural aging process during which an individual's skin gradually loses its youthful appearance. Aging skin is characterized by loss of volume, decreased elasticity, and increased laxity. Various aesthetic techniques are used in an attempt to reverse or slow the aging process. As such, individuals are increasingly undergoing rejuvenation procedures of the face. After facial procedures, they often notice that the improved appearance of the face is discordant with that of the untreated aging neck and chest. The chest and neck are exposed to substantial ultraviolet (UV) radiation and both regions tend to demonstrate photoaging. Additionally, the chest skin of females is vulnerable to the mechanical stress of the weight and movement of breasts.[1] Moreover, women are more prone to aging in this area as a result of hormonal changes relating to menopause and estrogen deficiency. These changes result in an accelerated breakdown of collagen and elastin, leading to skin thinning and laxity, and worsening of lines and wrinkles.[1] Aging of the skin in the décolleté region manifests as atrophy, laxity, wrinkles, and dyspigmentation.

Special anatomic considerations exist when treating the skin of the décolleté. The skin in this area is thinner than some areas of the face [2] as well as the arms and legs.[1] Additionally, there are over 13 times fewer hair follicles on the chest than on the lateral forehead.[3] This difference in pilosebaceous units contributes to slower healing and increased risk of scarring after aesthetic treatments of the décolleté region, particularly with ablative treatments.[4] Modalities used to treat signs of aging in the décolleté region include neurotoxins, fillers, chemical peels, intense pulsed light, non-ablative and ablative lasers[4] and microfocused ultrasound with visualization.[5]

Physicians use a variety of topical cosmeceuticals, energy-based devices, and injectable implants (including Radiesse®) to rejuvenate the décolleté region. In most cases, the use of energy-based devices and injectable implants is off-label use. Injectable implants, or dermal fillers, are primarily classified as permanent (i.e., non-biodegradable) and non-permanent (i.e., biodegradable) products. Permanent dermal fillers are now seldom used for this indication given the documented higher risk of severe and persistent adverse effects.[6] Non-permanent (i.e., biodegradable) dermal fillers include: hyaluronic acid (HA); collagen (bovine, porcine, and human); poly-L-lactic acid; calcium hydroxylapatite (CaHA; as in Radiesse); subject's own body fat (autologous fatty tissue); and dextran beads in HA.[6-8] Non-permanent dermal fillers are safer than permanent fillers and are usually associated with a low incidence of complications.[9]

Radiesse in its original undiluted form is indicated for aesthetic procedures, including deep dermal and subdermal soft tissue augmentation of the facial area and is also intended for restoration and correction of facial volume loss (see the current version of the Radiesse Instructions for Use [IFU]). Moreover, diluted Radiesse has been proven to improve skin texture and skin thickness.[1] Radiesse diluted with either lidocaine or saline (Radiesse:solvent, from 1:1 up to 1:6) has been shown to induce remodeling of the

extracellular matrix after subdermal injection, resulting in skin tightening and increased skin thickness.[1, 10] These alterations have been histologically associated with increased collagen and elastin production.[10, 11] Moreover, the treatment with diluted Radiesse has shown to be safe and was only associated with minor side-effects that are mostly transient and easily managed [12], thus representing an adequate injectable to address décolleté wrinkles. Dilution appears to allow a more homogeneous distribution of the material that may help to avoid complications such as granuloma formation.[13]

6.2 Study Rationale

The current study is designed to demonstrate the safety and effectiveness of diluted Radiesse for the correction of moderate to severe wrinkles in the décolleté.

Current available scientific, pre-clinical, clinical, and post-marketing surveillance data of Radiesse in a non-diluted form support and demonstrate the effectiveness and safety of the product.[14-17] Highly viscoelastic, Radiesse is well-suited for supraperiosteal, subdermal, and deep-dermal placement and can deliver a considerable volumizing effect. However, it is common practice among physicians to use Radiesse in a diluted form to address skin wrinkling in areas with a broader surface such as hands, neck, and décolleté.[1, 18] Dilution renders the product less viscous and therefore more suitable for rejuvenation treatments of larger areas without its volumizing effect. Diluted Radiesse has been shown to be effective and safe for the treatment of atrophic hands.[18, 19] Noticeable improvements in skin firmness and appearance after injection of Radiesse diluted with small amounts of lidocaine have been reported in the arms, abdomen, and thighs.[20, 21] Stimulation of dermal regeneration has also been established in several clinical studies.[10, 22, 23] Improvement in skin elasticity and pliability, and increased dermal thickness correlate with visible aesthetic improvements and subject satisfaction.

Because of the widespread interest of physicians to use Radiesse off-label in a diluted form, consensus recommendations were established in 2018 including face, neck, and décolleté.[24] The current study will attempt to confirm the effectiveness and safety of diluted Radiesse injection in the décolleté.

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6.3 Potential Benefits and Risks

The potential benefit associated with the use of Radiesse is the correction of moderate to severe wrinkles in the décolleté. Radiesse treatment of the décolleté contributes to an improvement of skin elasticity, thickness, density, and microstructure in the décolleté.

Furthermore, treatment with Radiesse provides high long-term patient satisfaction.[11, 28, 29]

Injection with Radiesse is less invasive than currently available aesthetic treatment options (e.g., plastic surgery) and provides a non-surgical option for patients. Its additional benefits over HA fillers include longer lasting results and enhanced cellular and extracellular matrix proliferation.[11, 29] Unlike permanent surgical implants, CaHA is a biodegradable material [30]; therefore, potentially undesirable effects such as overcorrection of the treated area subside spontaneously after a few months.

Regarding potential risks, treatment site responses associated with Radiesse consist mainly of ecchymosis, edema, erythema, pain, pruritus, discoloration, tenderness, local infection, and nodule development. In previous studies, common injection-related reactions have been transient and generally resolved within seven days of treatment. Less common, but possible side effects also include product migration, overcorrection, reactivation of herpes virus, persistent swelling, persistent nodules, and/or serious infection.

Adverse events (AEs) 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 with Radiesse. The following events have been identified due to a combination of their seriousness, frequency of reporting, or potential causal relationship with Radiesse: infection, cellulitis, impetigo, loss of effect, product displacement/migration, allergic reaction, anaphylaxis, hives, rash, pruritus, urticaria, angioedema, inflammation, necrosis, granuloma, nodules, induration, erythema, skin discoloration, pustule, skin pallor, hair loss, paresthesia, ptosis, pain, headache, swelling, asymmetry, abscess, temporary scabs, herpetic infection (including herpes simplex and herpes zoster), hematoma, blanching, blistering, dizziness, festoons, flu-like symptoms, Guillain-Barre syndrome, tachypnea, ischemic reaction, lymphoid hyperplasia, nausea, pericarditis, scarring, sensitivity to cold, vascular occlusion/obstruction, vascular compromise, ocular ischemia, diplopia, visual impairment/blindness, facial muscle paralysis, and Bell's palsy.

In clinical trials with Radiesse, reported AEs were generally as expected for a dermal filler, mild in nature, and transient in duration.[31-33] Long-term follow-up studies confirmed the favorable safety profile of Radiesse with primarily mild, injection-related side effects.[14] Immunologic reactions due to CaHA occur very rarely compared to permanent filler materials.[31-33] The treatment with diluted Radiesse has been previously documented as safe.[1, 10, 12, 24, 34]

In a 52-weeks pilot study conducted by the sponsor in Germany, 33 female subjects received three injections of diluted Radiesse (2:1 Radiesese:saline) with cannula in the décolleté area (M930521001). The study demonstrated an acceptable AE profile for these subjects, with no treatment-related SAEs reported. CCI

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[redacted]

CCI No AEs were identified that were unexpected or atypical with Radiesse use. No events associated with vascular occlusion, or pulmonary embolism or pneumothorax were reported.

In this current study, diluted Radiesse will be injected in the subdermal plane in the décolleté area using a blunt-tip, 22 gauge, flexible 2″ cannula. As shown by the lack of reports in the pilot study, the likelihood of intravascular injections leading to product embolization to the pulmonary vasculature is exceptionally low when diluted Radiesse is injected in the subdermal plane with a cannula. Similarly, the likelihood of penetrating the thoracic wall and causing a pneumothorax with a flexible cannula is minimal. Risks will be further minimized or reduced by monitoring the subject during the treatment procedure and for at least 30 minutes post-treatment.

Additional risks that may arise in the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency) may affect clinical study conduct. The sponsor's primary goal is to ensure the protection of the safety and well-being of the participating subjects. Potential challenges associated with a pandemic disease outbreak may include: quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations (e.g., if site personnel or trial subjects become infected with SARS-CoV-2). These challenges may lead to difficulties in meeting protocol-specified procedures and result in protocol modifications. This has been addressed for this study in Section 11.1.3.

Considering all risks and benefits, the potential benefits to subjects seeking treatment with diluted Radiesse outweigh the potential risks. The benefit/risk ratio of the device is considered acceptable when used on subjects seeking improvement in the appearance of décolleté wrinkles.

Additional information on device- and procedure-related contraindications, warnings, and precautions can be found in the current version of the commercially approved Radiesse IFU.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Objectives

Effectiveness

- Confirm the effectiveness of treatment with diluted Radiesse for correction of moderate to severe décolleté wrinkles by demonstrating superiority versus untreated-control.

Safety

- Demonstrate the safety of repeat treatment with diluted Radiesse for correction of décolleté wrinkles.

7.2 Endpoints

7.2.1 Effectiveness Endpoints

All endpoints will be assessed separately for the diluted Radiesse treatment group and the untreated-control/delayed-treatment with diluted Radiesse group, if not otherwise specified in Section 13. An overview of effectiveness endpoints is provided in Table 1.

7.2.1.1 Primary Effectiveness Endpoint

- Proportion of responders at Week 24 on Merz Aesthetic Scale (MAS) Décolleté Wrinkles-At Rest, as assessed live by a blinded evaluator, where response is defined as at least 1-point improvement from baseline.

7.2.1.2 Secondary Effectiveness Endpoint

- Proportion of responders at Week 24 on MAS Décolleté Wrinkles-Dynamic, as assessed live by a blinded evaluator, where response is defined as at least 1-point improvement from baseline.

- Proportion of subjects with any improvement, defined as a rating of + 1, + 2 or + 3 on Subject Global Aesthetic Improvement Scale (GAIS) at Week 24.

- Proportion of subjects with any improvement, defined as a rating of + 1, + 2 or + 3 on Investigator GAIS at Week 24.

7.2.1.3 CCI

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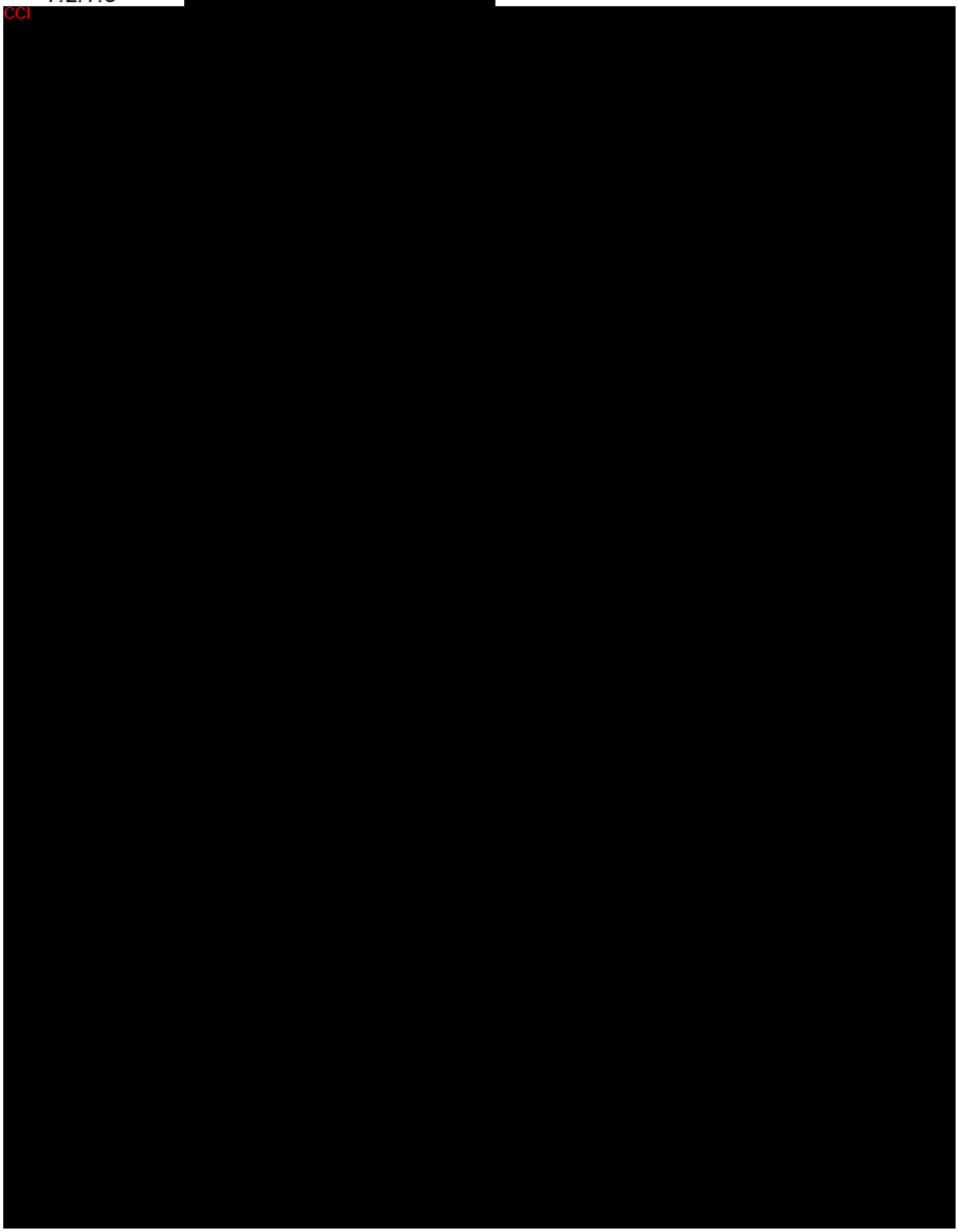

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Table 1: Effectiveness Endpoints Overview

Effectiveness endpoint	Description	Evaluator	Time point[1]	Assessment
Primary	Proportion of responders with at least 1-point improvement from baseline on MAS Décolleté Wrinkles-At Rest	Blinded evaluator	Week 24	Live
Secondary	Proportion of responders with at least 1-point improvement from baseline on MAS Décolleté Wrinkles-Dynamic	Blinded evaluator	Week 24	Live
Secondary	Proportion of subjects with a rating of + 1, + 2 or + 3 on sGAIS	Subject	Week 24	Photographs
Secondary	Proportion of subjects with a rating of + 1, + 2 or + 3 on iGAIS	Treating investigator	Week 24	Photographs

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[redacted]

CCI

[redacted]

7.2.2 Safety Endpoints

7.2.2.1 Secondary Safety Endpoints

- Incidence of TEAEs related to treatment with diluted Radiesse, as reported by the treating investigator throughout the study.

7.2.2.2 CCI

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[redacted]

8 CLINICAL INVESTIGATION PLAN

8.1 Overview of Study Design

This is a prospective, multicenter, randomized, evaluator-blinded, parallel-group study with a main period and a safety follow-up period, designed to evaluate the effectiveness and safety of subdermal implantation of diluted Radiesse for the correction of moderate to severe décolleté wrinkles. Healthy female subjects aged 30 to 65 years at the time of screening, CCI [redacted] will be eligible for enrollment. CCI [redacted] The treating investigators that will participate in the study are board-certified dermatologists and/or plastic surgeons.

All eligible subjects will be randomized at a 3:1 ratio to treatment with diluted Radiesse (Group A) or to untreated control followed by delayed treatment with diluted Radiesse (Group B). CCI [redacted] Subjects will be followed for CCI [redacted] up to Week 84 CCI [redacted]

Subjects in Group A will receive three treatments in total at Day 1, Week 6, and Week 12. Additionally, subjects in Group A will have the option for one additional retreatment at Week 36. CCI [redacted]

Subjects in Group B will receive three treatments upon completion of all effectiveness assessments at Week 24. CCI [redacted] Untreated-control/delayed-treatment subjects will not be offered an additional optional retreatment.

CCI [redacted] Subjects will have a screening period of up to 10 days. All enrolled subjects will participate in the study for a maximum duration of 84 weeks (± 14 days).

The primary effectiveness endpoint, the proportion of responders on MAS Décolleté Wrinkles-At Rest, will be assessed live by a blinded evaluator at Week 24 and compared to baseline. Response is defined as at least 1-point improvement from baseline. Standard safety parameters will be monitored throughout the study. CCI [redacted]

[redacted] provides an overview of the visit schedule and the study design. [redacted] details a Schedule of Events for each visit.

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

As detailed in Section 8.1, this is a prospective, multicenter, randomized, evaluator-blinded, parallel-group study. The study will be conducted at up to ten sites in the US. This multicenter design approach will increase the representativeness of the study results and decrease site-related biases. Randomization will eliminate selection bias in treatment assignment.

Since no approved, marketed products are currently available in the United States (US) for treatment of the décolleté region, an untreated-control group will be used for this study. To maximize the number of subjects exposed to acquire adequate safety data, control subjects will receive a delayed treatment with diluted Radiesse upon completion of all Week 24 effectiveness assessments.

The study duration of 84 weeks (i.e., main period and safety follow-up period) represents a reasonable timeframe to assess effectiveness as well as delayed-onset and/or long-term AEs.[14, 17, 33] A sequence of three treatment sessions at intervals of 6 weeks was chosen based on the pilot study and on the assumption that significant increases of collagen Type I and III are demonstrated at 4 to 9 months after treatment with diluted Radiesse. Published results suggest a cycle in which the highest deposition of new collagen and elastin occurs around 4 months after injection, with stability achieved by 9 months.[10, 23, 29, 35-37] Therefore, treatment intervals of 6 weeks were chosen, and an observation of 12 weeks after the last injection (24 weeks following initial injection), which corresponds with the effectiveness follow-up established by the consensus guideline.[24] Subjects randomized to treatment at Day 1 will also be eligible for optional retreatment at Week 36 to achieve further aesthetic décolleté enhancement. [redacted]

Dilution ratio and volumes to be administered in this study (see Sections 10.5.1.2 and 10.5.1.5) represent a safe standard for décolleté treatment based on the consensus guidelines for the injection of diluted Radiesse for skin tightening.[24] As recommended by the consensus guideline for the majority of individuals and as supported by the pilot study, 1.5 mL CaHA diluted 1:2 with physiologic saline solution was chosen as an average indicated volume and dilution. [redacted]

The injection technique follows the consensus guidelines mentioned above and is supported by the pilot study data: diluted Radiesse is to be injected in the subdermal plane of the décolleté area using linear threading and/or fanning retrograde technique. The use of a cannula rather than a needle improves the safety profile of the treatment and minimizes the risk of AEs, while providing delivery of the product in a manner analogous to that

achieved with a needle. [redacted]

9 STUDY POPULATION AND RESTRICTIONS

9.1 Number of Subjects and Sites

Approximately 152 subjects will be randomized at up to ten study sites in the US. [redacted], approximately 120 evaluable subjects are planned for this study.

All enrolled subjects will participate for a maximum duration of 84 weeks (± 14 days). All subjects will sign and date the ICF before randomization and before any study-related procedures are undertaken.

[redacted]

In general, discontinued subjects will not be replaced. In case of more than 10% missing primary effectiveness data due to a public health emergency (e.g. COVID-19), additional subjects can be randomized.

Additional information regarding subject enrollment and randomization is provided within the sample size justification in Section 13.1.

9.2 Selection of Subject Population

The selection criteria have been chosen to identify a suitable population of subjects to investigate the study objectives and to minimize safety concerns in this population.

9.2.1 Inclusion Criteria

To be eligible for study participation, each subject must meet all the following criteria:

1. Female ≥ 30 and ≤ 65 years old at the time of the screening.
2. Subjects seeking improvement of décolleté wrinkles.

[redacted]

CCI

[redacted]

9.2.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible to participate in the study:

CCI

[redacted]

5. Any previous surgery, including plastic surgery or permanent surgical implant in the treatment area.

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[redacted]

7. Previous treatment with collagen fillers, CaHA (e.g., Radiesse), and/or long-lasting HA fillers (e.g., Belotero® Intense/Volume, Juvéderm® Volift/Volbella) in the décolleté within the past 24 months.

CCI

[redacted]

9. Previous treatment with botulinum toxin, ablative or fractional laser, microdermabrasion, microneedling, chemical peels, and/or non-invasive skin

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[redacted]

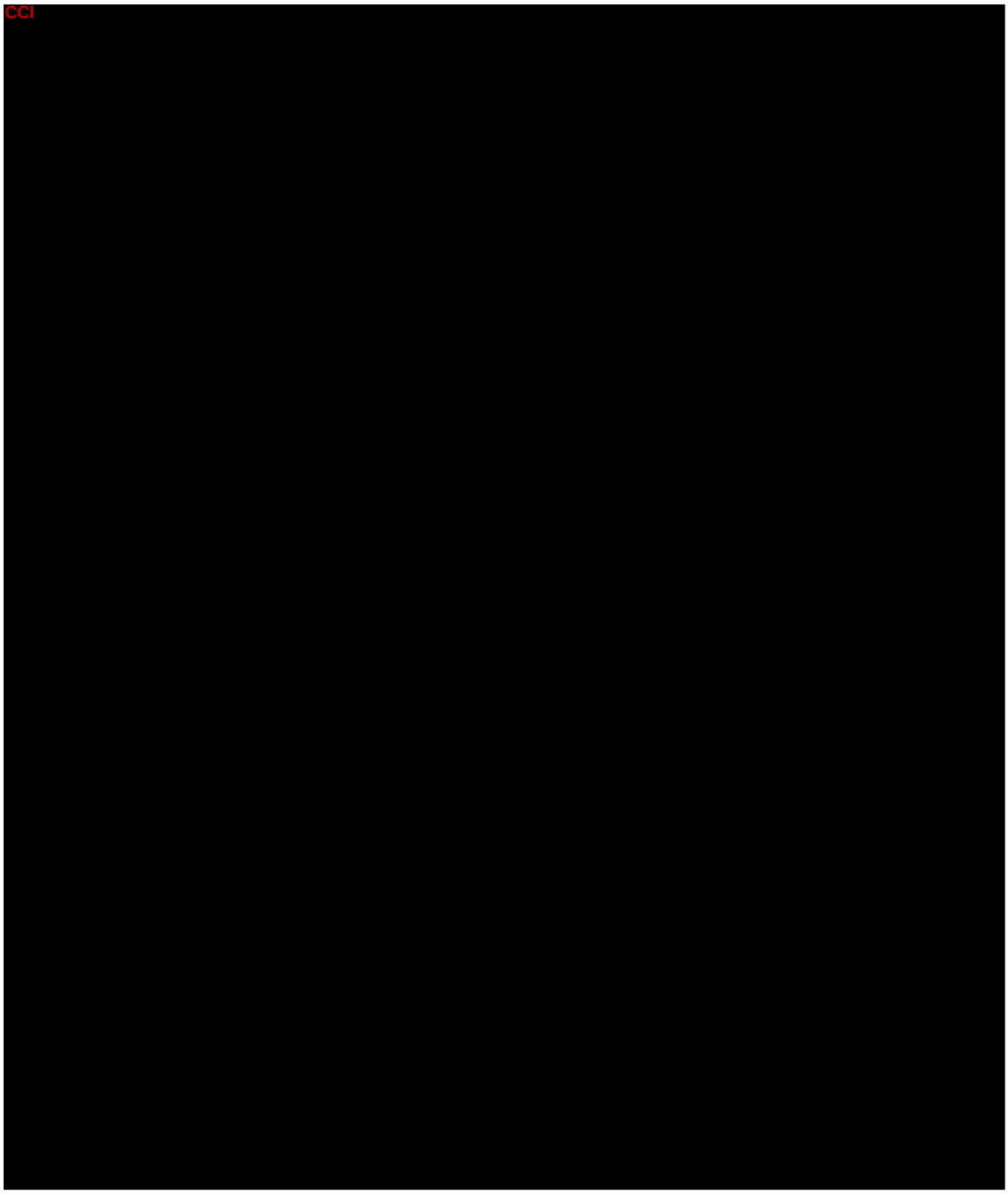
tightening (e.g., ultrasound, radiofrequency, intense pulsed light treatment) in the décolleté within the past 6 months.

CCI

[redacted]

CCI

[redacted]



9.2.4 Subject Enrollment and Randomization

Subjects are considered to be enrolled when they provide informed consent (i.e., sign the ICF) and meet all eligibility criteria. Eligible subjects will be randomized at the screening visit.

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 study (screen failure) may not be rescreened.

9.2.6 Removal of Subjects from Therapy or Assessment

9.2.6.1 Treatment Discontinuation

If study treatment is discontinued at any time during the study, the investigator will record the reason for treatment discontinuation in the study records. Potential reasons for discontinuation of treatment may include refusal by the subject to receive additional treatments or physician's decision. The investigator may request that a subject discontinuing treatment continue to participate in the study and complete all remaining visits and assessments for safety follow-up. For subjects who decline to continue study 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 the study, or until the sponsor decides to terminate the study, whichever comes first. The only reasons a subject will not be followed for all scheduled visits include withdrawal of consent, continuous non-compliance with protocol requirements, or loss to follow-up (e.g., moving away from study 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 study at any time at her own request without prejudice. 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 study visit, the following actions will be taken:

- The site will attempt to contact the subject at least twice and reschedule the missed visit as soon as possible. Every effort to regain contact with the subject will be made (e.g., telephone contact on different dates/times, registered mail). All contact attempts will be documented.

- If attempts to contact the subject are not successful, then the subject will be considered lost to follow-up and discontinued from the study.

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 Study/Early Termination visit specified in the Schedule of Events (Section 11.1 and [redacted] while fully respecting the subject's rights.

If a non-serious AE is unresolved at the time of the subject's final study 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 serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) to resolution. Information on pregnancy and the outcome for any female who becomes pregnant during the study will be collected.

9.2.6.3 Provision of Care for Subjects after Study Discontinuation

The investigator is responsible for ensuring the adequate and safe medical care of subjects during the study. After end of the study or after subject discontinuation, the sponsor will follow all applicable local or international regulations and guidelines with regard to follow-up care for subjects. The investigator will ensure that appropriate consideration is given to a subject's post-study care.

9.2.7 Suspension or Premature Termination of a Study Site

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

- Investigator request;
- Serious or persistent noncompliance with the protocol, local regulations, and/or 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.

In the event of a pandemic disease outbreak, (e.g., new COVID-19 public health emergency), it might not be feasible for a study site to continue participation. In this scenario, consideration will be given to the effect of the study site closure on the safety and well-being of participating subjects. Additionally, the impact on and maintenance of data validity should be considered in the event of study site closure(s).

9.2.8 Suspension or Premature Termination of the Study

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

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

- Determination of a potential safety risk to subjects, including intravascular injection, necrosis, vision loss, stroke, pneumothorax, pulmonary embolism, and/or myocardial infarction;
- Inadequate subject enrollment;
- Decision by the IEC/IRB to suspend or terminate approval/favorable opinion for the study; 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 temporarily suspend enrollment and treatment at the investigative site where the risk was identified. A root cause investigation will be conducted to determine the cause of the event and whether the risk could have been anticipated (e.g., lack of compliance with planned treatment) or if the identified risk was unanticipated. If the risk is determined to be unanticipated, the sponsor will suspend the entire trial while the risk is further assessed and preventive, correcting measures are designed and implemented. 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.

In the event of premature study suspension or termination for any reason, the sponsor will inform all investigators and relevant regulatory authorities promptly of the study 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, local, and international guidelines and regulations.

In the event of a public health emergency the sponsor will inform all investigators, the IEC/IRB, and the relevant regulatory authorities promptly of any planned mitigations to protect the safety and well-being of subjects. This can include but is not limited to: putting the study recruitment on hold, stopping or postponing further treatments or changing on-site visits to visits by phone or at another clinical site (e.g., if the primary site is closed due to quarantine).

9.2.9 End of Study

The end of the study is defined as when the last subject completes the last visit and the database is closed [CCI redacted]

10 STUDY DEVICE AND TREATMENT OF SUBJECTS

10.1 Description of Study Device

Radiesse injectable implant (Unique device identifier [UDI]: M2138071C0K15) is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principal component is synthetic CaHA suspended in a gel carrier consisting of glycerin, sodium carboxymethylcellulose and sterile water for injection. Radiesse injectable implant (1.5 cc) has a CaHA particle size range of 25 to 45 µm.

Radiesse is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, for hand augmentation to correct volume loss in the dorsum of the hands and is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus (HIV). In the current study, the intended use of Radiesse is subdermal implantation for the correction of moderate to severe décolleté wrinkles.

CCI [redacted]

10.2 Instructions for Use and Administration

Radiesse should be used in the décolleté treatment region according to the information and instructions presented in Section 10.5. Additional information on product usage is provided in the product labeling (current version of the commercially approved Radiesse IFU).

Radiesse should only be administered by the treating investigators. All treating investigators that will participate in the study are board-certified dermatologists and/or plastic surgeons.

10.3 Methods of Assigning Subjects to Treatment Groups

Subjects who provide informed consent, complete all screening assessments, meet all eligibility criteria, and are accepted for enrollment into the study will be assigned a subject identification number.

Treatment group assignments will be made based on the study randomization scheme.

CCI [redacted]

Please see Section 13.2 for additional randomization details.

10.4 CCI [redacted]

CCI [redacted]

10.5 Study Treatment

All protocol-specific criteria for the administration of study treatment must be met and documented prior to administration of any study treatment. All device administration will be performed on site by the treating investigator. Subjects will not be dispensed any investigational material.

10.5.1 Planned Treatment Regimen

10.5.1.1 Décolleté Treatment Region

Subjects will receive treatment with diluted Radiesse with a cannula for the correction of moderate to severe décolleté wrinkles.

CCI [redacted] illustrates the décolleté treatment region that comprises approximately 100 cm^2, and is delineated superiorly by the sternoclavicular notch, laterally by the midclavicular line and inferiorly by the superior point of the intermammary cleft. No injections are to occur in an area overlying or including breast tissue.

CCI [redacted]

10.5.1.2 CCI [redacted]

CCI [redacted]

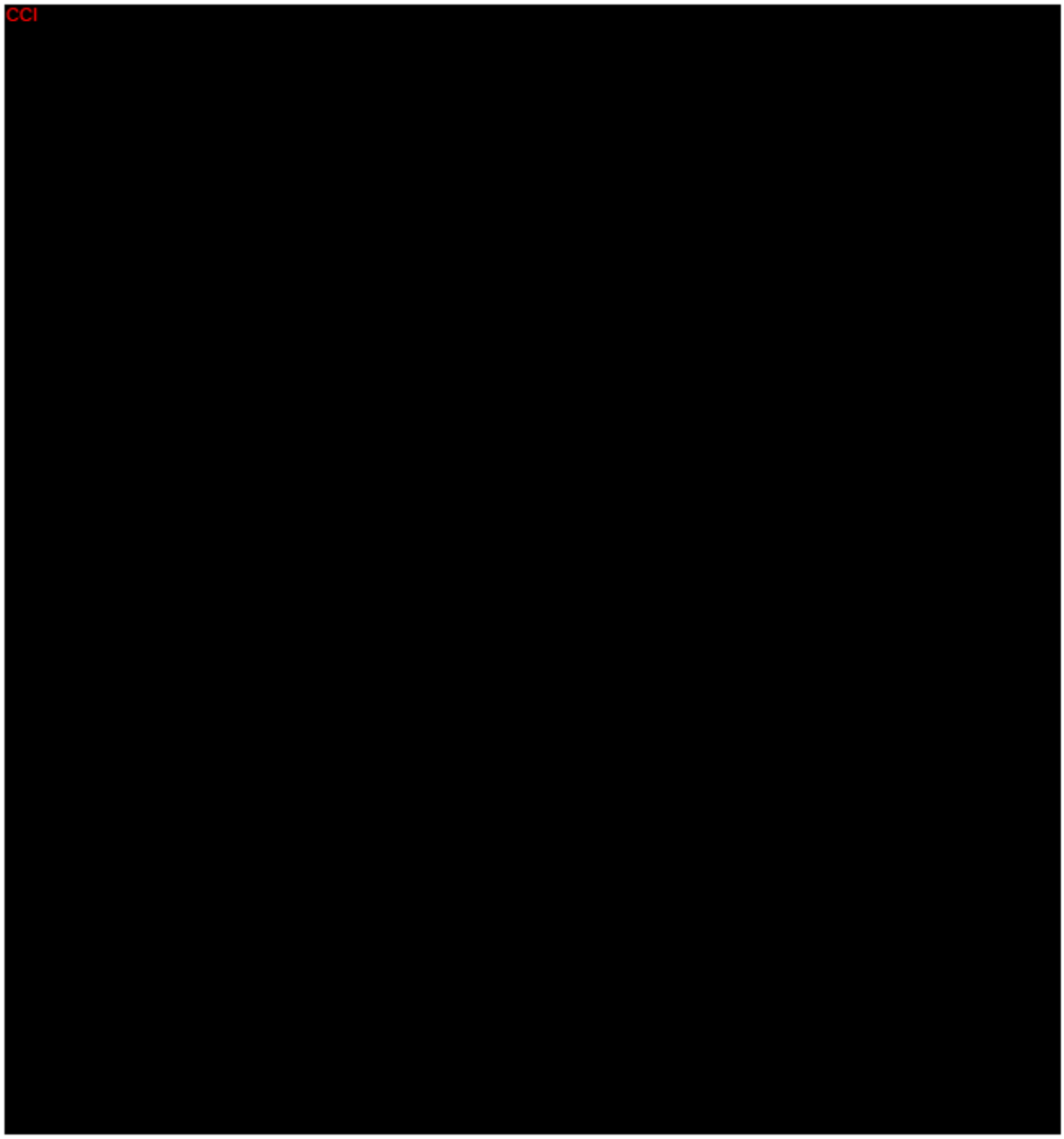
10.5.1.2.1 CCI [redacted]

CCI [redacted]

CCI

10.5.1.2.2 CCI

CCI



10.5.1.3 Treatment Area

After ensuring that the treatment area has been thoroughly cleansed, the area should be swabbed with alcohol or other antiseptic. Supplementary topical or intradermal anesthesia may be used for additional pain management before the injection at the discretion of the treating investigator.

Diluted Radiesse will be administered subdermally via a 22G 2-inch (50 mm) blunt-typed cannula utilizing the linear threading and/or fanning retrograde technique CCI

CCI [redacted]

10.5.1.4 CCI [redacted]

CCI [redacted]

10.5.1.5 CCI [redacted]

CCI [redacted]

CCI

[redacted]

10.5.2 Selection and Timing of Treatment for Each Subject

For subjects randomized to the treatment group (Group A), treatment will occur at Day 1, Week 6, and Week 12. Subjects in Group A may receive an optional retreatment at Week 36 to achieve optimal cosmetic results, at the discretion of the treating investigator and the subject.

For subjects randomized to the delayed-treatment group (Group B), treatment will occur at Weeks 24, 30 and 36.

In the event of a public health emergency, further treatments may be halted or postponed.

10.6 Prior and Concomitant Therapy

Previous therapies received prior to enrollment and concomitant therapies, including pre- and post-treatment pain measures, should be documented in the eCRF.

Restrictions regarding concomitant therapy are discussed in detail in Sections 9.2.2 (Exclusion Criteria) and 9.2.3 (Restrictions during the Study).

10.7 Study Supplies and Packaging of Treatment Supplies

Radiesse will be provided by the sponsor. The sponsor or designee will package study 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 is to be used exclusively for treatment of subjects randomized in this study and will be labeled as follows: "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use." Device labels will also note the manufacturer name and address and the quantity within the package. A copy of the current version of the commercially approved Radiesse IFU will be provided with each IMD.

CCI

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), considerations may be made to supply study sites with sufficient study supplies to prevent supplying disruptions during the outbreak.

10.8 Receipt, Storage, Dispensing, and Return

Upon receipt, the site personnel will verify the contents of all study supplies received and promptly notify the appropriate contacts of any discrepancies or damages. The investigator is responsible for ensuring that an accurate record of inventory is maintained. The investigator or designee will keep a current record of the study device delivery to the study site, inventory, and dispensing, and this record will be made available to the sponsor upon request. Study sites will be queried about any discrepancies.

All study devices must be stored in a secure, environmentally controlled, monitored area in accordance with the labeled storage conditions (see Section 10.1 and the current version of the Radiesse IFU).

Only authorized study personnel may supply, dispense, and/or administer study treatment, and only subjects randomized in the study may receive study treatment. The investigator is responsible for maintaining a current, accurate record of all study-treatment dispensation.

Any used cannulas should be discarded per the appropriate handling and disposal procedures at the site. Any used, partially used or unopened IMD, unopened cannulas, and/or outer packaging should be retained so the monitor can perform device-accountability procedures.

At the end of the study and after verification of study device accountability, it is the investigator's responsibility to return all unused study supplies, as directed by the sponsor. Appropriate records of return must be maintained for accountability purposes.

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

10.9 Device Accountability Procedures

The sponsor will provide the investigator with all necessary study supplies after approvals of the study protocol and ICF have been received from the IEC/IRB. Accountability for study supplies at the study site is the responsibility of the investigator.

Access to the IMD will be controlled, and the IMD will be used only in the clinical investigation and according to the clinical study protocol (CSP). The sponsor will keep records to document the physical location of all IMDs from shipment to the study sites until return. The investigator or an authorized designee is responsible for ensuring that accurate records of receipt, use, and return of the IMD, are maintained and include:

- The date of receipt and quantity of units received.
- Identification of each IMD (batch number/serial number or unique code).
- The expiry date (if applicable).
- The names of all persons who received each device.
- The dates and time of injection.
- Unique subject number.
- Date and quantity of units returned (if applicable). Include reason for return, if applicable.
- The date of return of unused, expired, or malfunctioning IMDs (if applicable).

All unused investigational products must be returned to the sponsor or designee immediately after the study is completed. Products accidentally destroyed during shipment or at a study site should be accounted for and documented. All clinical supplies must be accounted for at the termination of the study and a written explanation provided for discrepancies.

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), performing study-accountability procedures remotely should be considered and return of unused supplies may be delayed until return procedures can be safely performed by study site personnel.

10.10 Treatment Compliance

The three required study treatments will be administered by the treating investigator. Potential deviations from the defined study-treatment administration will be reported as protocol deviations.

10.11 Duration of Study

Subjects will have a screening period of up to 10 days. All enrolled subjects will participate for a maximum duration of 84 weeks (± 14 days).

In the event of a public health emergency the study might be halted, recruitment interrupted, and/or study processes and flow might be modified impacting the study duration and/or visit schedule depending on the study status at the time of the event. Mitigations may include, but are not limited to, extending visit windows, performing visits by phone or video, and/or performing effectiveness assessments remotely (see Section 11.1.3).

11 STUDY PROCEDURES

11.1 Visit Schedule

The investigation activities and visit schedule are detailed in the Schedule of Events CCI

The purpose of the screening visit (Visit 1) is to determine subject eligibility for participation in this study and must be completed − 10 to − 3 days prior to Day 1 (Visit 2). Eligible subjects will be randomized at the screening visit.

Subjects randomized to Group A will receive treatment at Day 1, Week 6, and Week 12. Group A subjects also have the option for one additional retreatment at Week 36. Subjects randomized to Group B will remain untreated until Week 24, when the primary effectiveness endpoint will be evaluated. Upon completion of all primary effectiveness assessments, Group B subjects will be treated (i.e., will receive delayed treatment) at Weeks 24, 30, and 36. Group B subjects will not be offered an additional retreatment.

All treatments should be administered at the study site by the treating investigator, occurring only after completion of all required pre-injection procedures and assessments CCI

CCI Safety follow-up will occur until Week 84 ± 14 days.

The primary endpoint visit will occur at Week 24 (± 7 days) CCI In the case of premature discontinuation of the study, a final assessment (End of main period visit) should be performed.

11.1.1 Scheduled Visits

All scheduled visits and applicable study assessments must occur as noted in Section 11.1 and the Schedule of Events [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 study visit should have that visit recorded as an unscheduled visit, during which concomitant medication/procedures, skin examination, and AEs must be assessed and recorded.

An unscheduled visit must be scheduled if entries in the subject diary require additional follow-up as determined by the investigator.

An unscheduled visit must be scheduled if information acquired from a subject during a post-treatment phone call requires additional follow-up as determined by the investigator.

11.1.3 Modified Visit Schedule during a Pandemic

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), the sponsor's primary goal is to ensure the safety and well-being of participating subjects. In general, the following recommendations apply if a pandemic disease outbreak occurs:

- In general, limit scheduled visits to those necessary for subject safety, clinical care, or follow-up of AEs.
- Use phone or virtual study visits for routine, mandated safety follow-up visits as described in the study protocol.
- Determine if effectiveness data can be collected remotely.
- Exercise flexibility when necessary and possible to continue performing protocol required procedures (e.g., subject imaging, photography, if applicable).

11.2 Study Assessments and Definitions

11.2.1 Effectiveness Assessments

The effectiveness of subdermal implantation of diluted Radiesse for the correction of moderate to severe wrinkles in the décolleté will be evaluated with several assessments. Refer to the respective endpoints (Section 7.2), visit schedule (Section 11.1), and Schedule of Events [redacted] for additional information on the methods and timing of effectiveness assessments.

11.2.1.1 CCI

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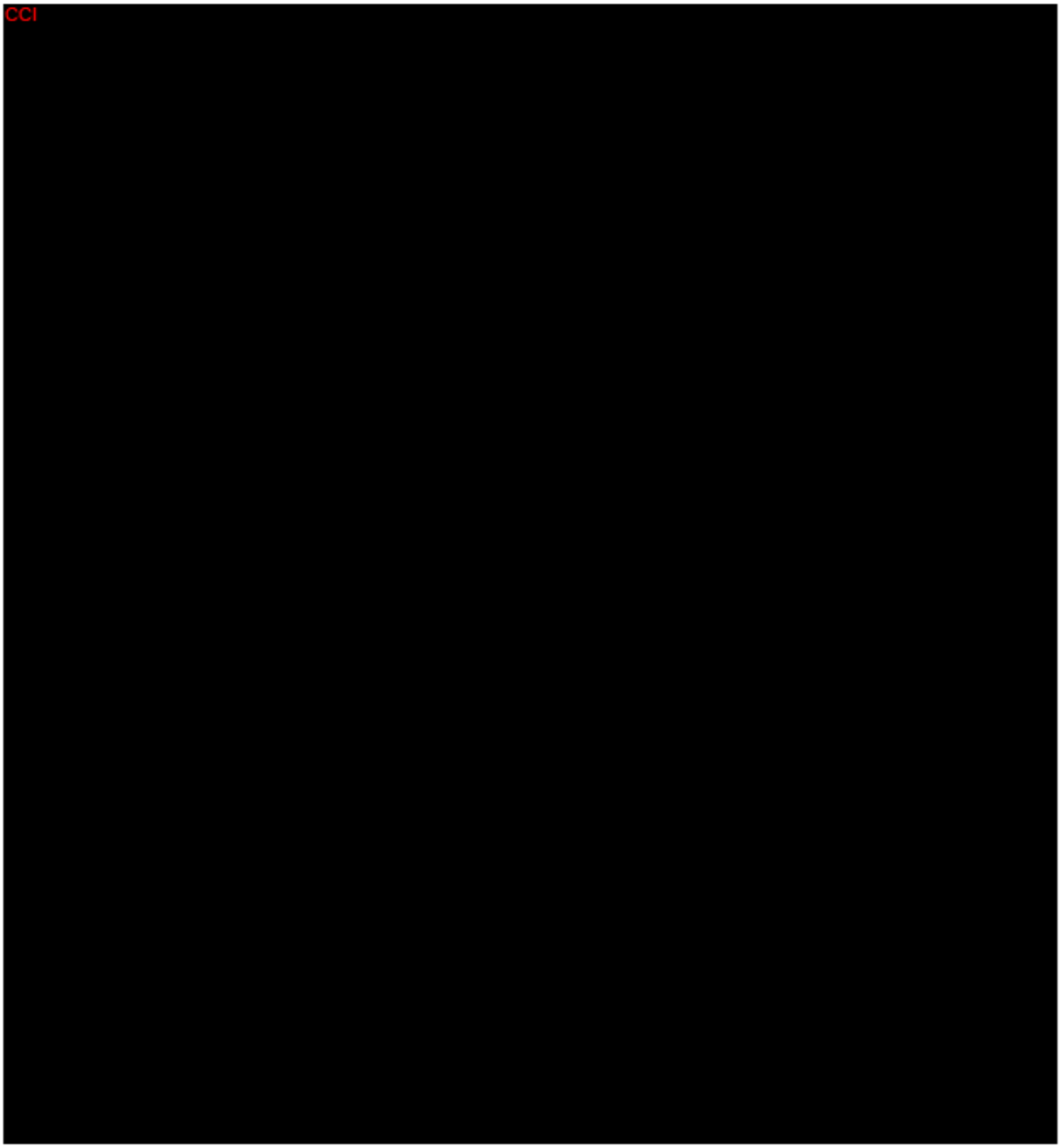

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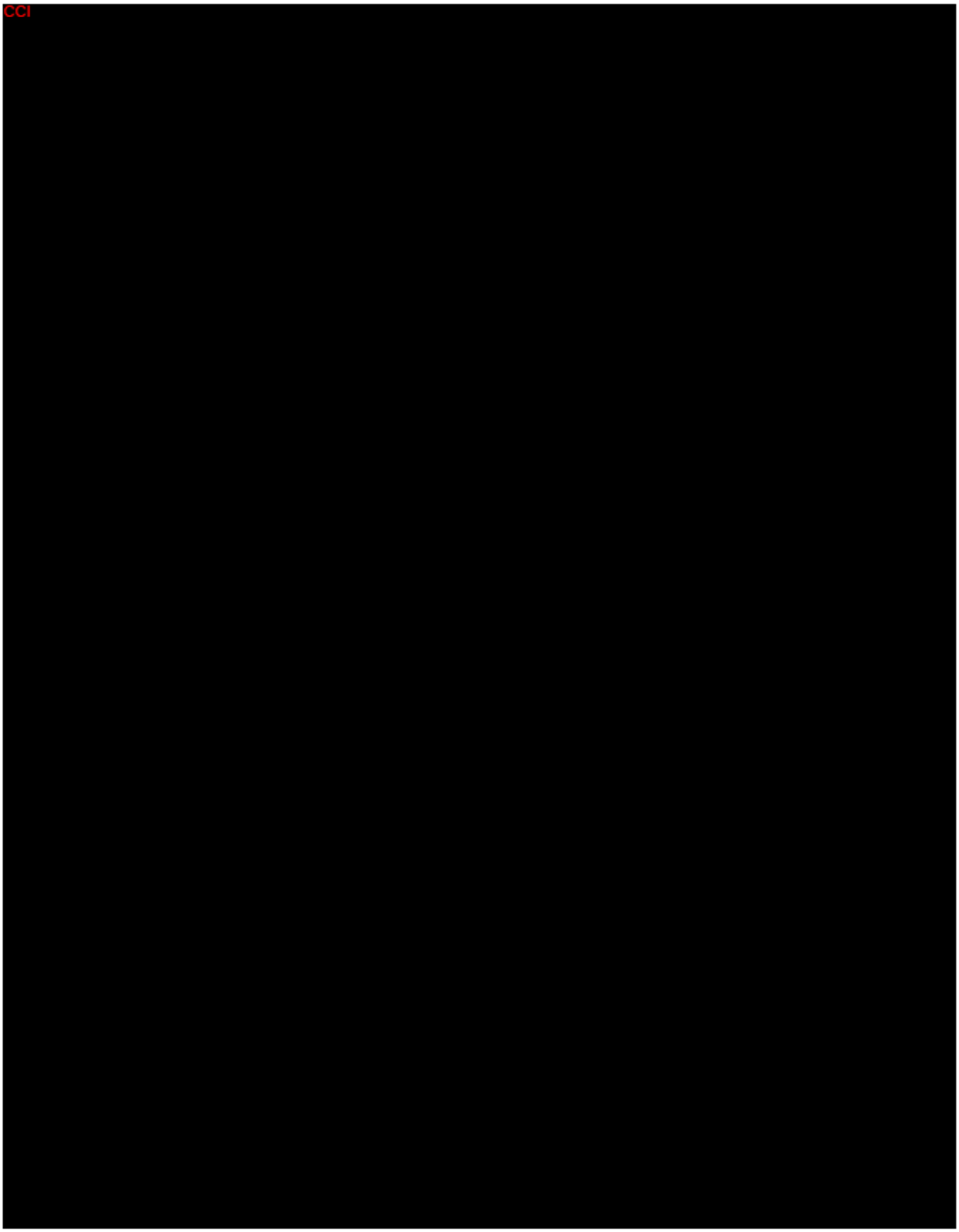
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11.2.1.9 CCI [redacted]

CCI [redacted]

11.2.2 Safety Assessments

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

Refer to the respective endpoints (Section 7.2.2), the Schedule of Events CCI [redacted] and the safety definitions (Section 12) for additional information on the safety assessments.

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

All AEs/SAEs reported by study subjects, investigators, or other study staff after the time of informed consent through end of study will be recorded, regardless of causality. The period of observation for an AE extends from signing of the ICF through the subject's last study visit. Additional information (e.g., definitions, reporting requirements) regarding AEs and SAEs is provided in Section 12.1 and Section 12.2, respectively.

Study subjects will be queried for the presence or absence of any visual symptoms at each follow-up visit CCI [redacted] If visual symptoms are reported at a follow-up visit, subjects will undergo visual function assessments to potentially identify ophthalmic signs and/or symptoms that may represent ophthalmic-artery occlusion as detailed in Section 11.2.2.2.3.

11.2.2.2 CCI [redacted]

CCI [redacted]

11.2.2.2.1 CCI [redacted]

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11.2.2.2.2 CCI [redacted]

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11.2.2.2.3 CCI [redacted]

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11.2.2.2.3.1 CCI

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11.2.2.2.3.2 CCI [redacted]

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11.2.2.2.3.4 CCI [redacted]

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CCI [redacted]

11.2.2.2.4 CCI [redacted]

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CCI [redacted]

CCI [redacted]

11.2.3 Additional Data Collected

Data for other assessments will be collected as follows:

- Demographics and other baseline characteristics;

CCI [redacted]

- Medical history/concomitant diseases; and

- Previous and concomitant medications and non-drug treatments.

For time points of all other assessments, refer to CCI [redacted]

11.2.4 Appropriateness of Assessments

The MAS Décolleté Wrinkles scales are currently the only clinical instruments shown to be valid and highly reliable in clinical grading of décolleté wrinkles in both the "At Rest" and "Dynamic" positions.[38] Using a psychometric evaluation process, 13 expert raters scored two sets of photographs from subjects presenting with a broad spectrum of age-related décolleté changes (e.g., wrinkling). This analysis demonstrated that subject scores on both MAS Décolleté Wrinkles scales were positively correlated with subject age (actual and estimated) and the estimated degree of treatment effort needed to produce aesthetic improvement. Further, both MAS Décolleté Wrinkles scales demonstrated substantial degrees of intra- and inter-rater reliability in the pool of expert raters. These findings demonstrate that the MAS Décolleté Wrinkles scales are valid in terms of content and structure and establish a threshold for treatment benefit.

CCI [redacted]

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 abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the IMD.

Note:

1. This definition includes events related to the IMD.
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 study 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 in the AE eCRF. Any observed AE will be fully investigated, documented, and followed until the event is either resolved or adequately explained. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered 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.

Pre-existing conditions 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 collected during each clinical study visit based on the subject's spontaneous description, through investigator inquiry, or upon discovery in the course of examinations completed during the visit. The investigator will assess and record any AE in detail in the subject file and on the AE eCRF. The following information must be recorded:

- AE diagnosis or main symptom;
- Affected treatment area: In case of a local reaction, the corresponding area should be reported;

- Date of onset;
- Intensity (maximum observed using the Severity Grading scale; see Section 12.1.3);
- Causal relationship to IMD (not related, related);
- Causal relationship to procedure (not related, related);
- Serious (yes or no), date serious since, and reason for seriousness;
- Outcome (see Section 12.1.5);
- AE leading to discontinuation of the clinical study (yes or no);
- Action taken with medical device; and
- Stop date.

In cases of a SAE (defined in Section 12.2), the investigator must also complete an SAE Report Form and report it to the sponsor within 24 hours, 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 her 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 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 (ADE; Section 12.3). If the event is serious, it is a serious adverse device effect (SADE; 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:

- led to death;
- led to serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury;
  - a permanent impairment of a body structure or a body function, including chronic diseases;
  - inpatient or prolonged hospitalization; or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death, or a congenital abnormality or birth defect, including physical or mental impairment.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CSP, 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 not regarded as SAEs.

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

- suitable action had not been taken; or
- intervention had not been made; or
- 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 study period, whether considered to be related to an IMD or not, must be reported via fax, telephone, or e-mail, and an SAE Report Form should be submitted to the sponsor immediately upon knowledge of the event. Further reporting details will be outlined in a separate document.

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/study site identification); and/or
- An event or outcome that can be identified as serious.

The investigator must report SAEs to Merz as defined in Section 12.2 and the site's IEC/IRB per their reporting guidelines. Within 10 working days after Merz first receives notice of the SAE, Merz Product Safety will conduct an evaluation of the SAE and report the results of such evaluation to regulatory agencies, IECs/IRBs, and investigators, as applicable.

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 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 (including main and safety follow-up periods), any ongoing SAEs will be followed until resolution or stabilization under the responsibility of the investigator per his/her standard of care.

The investigator should complete and send any SAE Report Forms (including any follow-up forms) to Merz North America Product Safety via the email provided below:

Merz North America, Inc. Product Safety
6501 Six Forks Road
Raleigh, NC 27615
US

Product Safety Email: AxUS-adverse.events@merz.com

12.3 Definition of an Adverse Device Effect (ADE)

An ADE is defined as an AE 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)

A 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 Adverse Device Effect (UADE)

A UADE 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 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 performance.

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

12.6 Definition of Technical Complaint

A technical complaint, also referred to as a product complaint, is an apparent or suspected deficiency of a product in which the product does not meet its specification (e.g., leaking tube, incorrect consistency, cracked vial).

12.6.1 Reporting and Handling of Device Deficiencies and Technical Complaints

All device deficiencies and technical complaints shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by Merz North America, Inc.

The investigator will attempt to evaluate if the deficiency or complaint 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 and technical complaints:

- A device deficiency/technical complaint eCRF must be completed and submitted within 24 hours by the investigational site, irrespective of the seriousness of the case.
- A device deficiency/technical complaint eCRF must be completed and submitted by the investigational site, irrespective of whether the complaint led to an AE.
- If a technical complaint or device deficiency is associated with an SAE, the investigational site must also complete and submit an SAE Report Form (Section 12.2.2) in addition to the device deficiency/technical complaint eCRF.
- If a technical complaint or 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/technical complaint form, instead of the eCRF page, and send to the sponsor within 24 hours to both their clinical study representative

as well as to the Merz Technical Complaint Department for processing using the following email address: complaints2@merz.com.

The investigator should retain the device in question for future inspection and investigation by the sponsor, if necessary. The Merz Technical Complaint Department will decide if the device and/or supplies in question need to be returned and to whom they should be sent for investigation.

12.7 CCI [redacted]

CCI [redacted]

12.8 CCI [redacted]

CCI [redacted]

12.9 Reporting of Pregnancy

Any pregnancy that starts during the clinical study must be reported, using the Pregnancy Form, by the investigator to the sponsor within 24 hours of learning of its occurrence. 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 (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 study, the subject must not receive further treatments (i.e., additional treatments or optional retreatment); however, the subject will remain in the study.

13 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of study planning. CCI [redacted]

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 of the main period. If needed, the SAP will be updated before database close after the safety extension period (including data of main and safety follow-up periods).

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

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), if on-site visits are not possible due to site closures, travel limitations, or other considerations (e.g., if site personnel or trial subjects become infected with SARS-CoV-2), the following mitigations should be considered and assessed in an updated SAP:

- Changes to planned and additional analyses due to the public health emergency should be described. Drop-out patterns and sources of bias such as missing values and virtual instead of live assessments (if applicable) should be thoroughly assessed.
- Systematic identification of protocol deviations due to the pandemic should be included.
- The need for involvement of an independent Data Monitoring Committee should be considered, particularly if trial sample size changes are anticipated.

13.1 Estimation of Sample Size

The primary effectiveness analysis considers the proportion of subjects with at least 1-point (≥ 1-point) improvement on the MAS Décolleté Wrinkles-At Rest scale at Week 24 compared to baseline as assessed live by a blinded evaluator. Subjects will be randomized into two treatment groups as detailed in Section 13.2.

CCI [redacted]

- Group ratio: 3:1;

CCI [redacted]

CCI

CCI approximately 152 subjects, 114 subjects in the treatment Group A and 38 subjects in the untreated-control/delayed-treatment Group B, will be randomized for this study. Regarding the safety evaluation, in a sample size of 152 subjects an adverse event with a true incidence of 1.5% will be observed at least once with a probability of 89.9%.

CCI

Sample size calculations CCI were performed using nQuery software (Version 8.5, Statistical Solutions Ltd., 2019).

CCI

13.2 Randomization

All eligible subjects will be randomized 3:1 to one of the following groups:

- Group A: Treatment with diluted Radiesse at Day 1, Week 6, and Week 12.
- Group B: Untreated control followed by delayed treatment with diluted Radiesse at Week 24 (after primary endpoint assessment), Week 30, and Week 36.

The randomization will be block-stratified by study site as described in Section 10.3.

13.3 Populations for Analysis

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

- The Safety Evaluation Set (SES) will consist of all subjects treated at least once. If not otherwise specified, subjects in the SES will be analyzed as treated.
- The Intent-to-treat (ITT) will include all randomized subjects. Subjects in the ITT analyses will be analyzed as randomized. This will be the primary population used for the effectiveness analyses.
- The Per Protocol Set (PPS) is a subset of subjects in the ITT without major protocol deviations potentially affecting statistical analysis. Final determination of what constitutes major or minor protocol deviations in this sense will be made prior to database close CCI

CCI

13.4 Analysis of Study Data

Effectiveness and safety endpoints are provided in Sections 7.2.1 and 7.2.2.

CCI [redacted] CCI [redacted] Adequate descriptive statistics will be provided for each endpoint, by randomized treatment group and overall, where appropriate. Metric descriptive statistics will comprise number of observations, mean, standard deviation, quartiles, minimum, median, and maximum. Frequency tables for qualitative endpoints/variables will display absolute and percent frequencies (n, %) per category where the denominator will be chosen according to the adequate analysis population. Ordered categorical data will be summarized by metric descriptive statistics and frequency tables, where appropriate. All variables will be analyzed as absolute data and as change from baseline assessment, as applicable. Summaries by categorical variables/groups should always include a 'Total' category.

Descriptive confidence limits and descriptive p-values will be given, where appropriate. If not otherwise specified, statistical tests will be conducted two-sided at type I error rate 5% and CIs will be two-sided with confidence level 95%. All data captured in the eCRF and all image analysis data will be listed.

13.4.1 Effectiveness Analyses

13.4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint (Section 7.2.1.1) will be summarized as counts and percentages for the treatment and control groups.

Two hypothesis tests CCI [redacted] will be performed, based on the primary effectiveness endpoint. These tests will be evaluated in a sequential order on the ITT. To control for multiplicity, a hierarchical-testing procedure will be performed at a one-sided α level of 0.025.

The first hypothesis of the primary analysis is to demonstrate that the response rate is statistically significantly larger than 50% in treated subjects. This 50% threshold is commonly used in aesthetic medical device studies to measure a meaningful response.

The second hypothesis is to show statistical superiority of treatment over untreated control. Both hypotheses will be tested using the lower limits of the 95% CIs (two-sided), based on Wilson scores. The lower limit of the 95% Wilson CI must exceed the margin of 50% responder rate to reject Hypothesis 1 (H_{10}). The lower limit of the 95% Newcombe CI must be greater than zero to reject Hypothesis 2 (H_{20}).

CCI

[redacted]

13.4.1.1.1 CCI [redacted]

CCI

[redacted]

CCI [redacted]

13.4.1.2 Secondary Effectiveness Endpoint

Treatment comparisons for the secondary effectiveness endpoint proportion of responders at Week 24 on MAS Décolleté Wrinkles Dynamic as assessed live by a blinded evaluator will be conducted analogous to the primary effectiveness endpoint. Descriptive two-sided 95% Wilson score based CIs, CCI [redacted] will be performed CCI [redacted].

The iGAIS and sGAIS assessments describing the overall impression of post-treatment aesthetic change specific to the décolleté compared to baseline photograph as well as percentage of subjects with improvement in iGAIS and sGAIS will be evaluated at Week 24 by baseline severity and in total. CCI [redacted] CCI [redacted]

13.4.1.3 CCI [redacted]

CCI [redacted]

CCI

[redacted]

13.4.2 Safety Analyses

All safety analyses will be performed on the SES.

All AEs and SAEs will be listed, including type, duration, severity, and relationship to the IMD.

Only TEAEs will be summarized CCI [redacted] using MedDRA preferred terms (PTs) within the system organ classes (SOCs). Safety analyses regarding TEAEs will be performed overall, for treatment Group A and Group B (delayed-treatment control) where appropriate.

Treatment-emergent AEs (TEAEs) are defined as AEs with onset or worsening at or after the first administration of study treatment. In this regard, an AE with onset prior to treatment that worsens at or after first administration of study treatment must be documented as a new TEAE with onset at the time of worsening.

CCI [redacted]

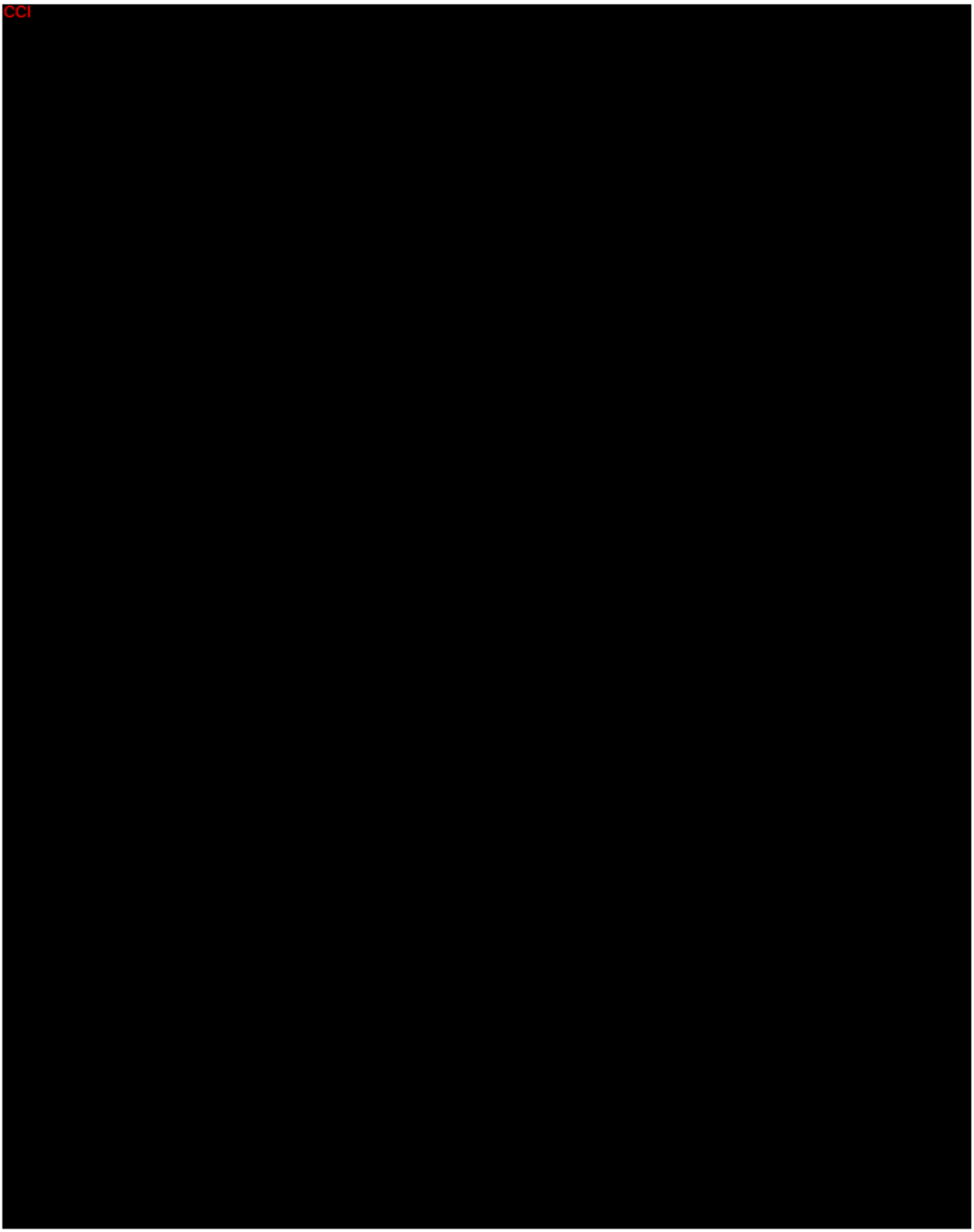
All other AEs that do not follow the prior definitions will be considered non-TEAEs.

13.4.2.1 Secondary Safety Endpoints

Incidences of TEAEs related to the treatment with diluted Radiesse will be summarized by treatment group and total, overall and by study period by PT and SOC.

13.4.2.2 CCI

CCI



CCI [redacted]

13.4.3 Other Subject Data

Study subjects will be characterized by descriptive statistics for:

- Disposition of subjects;
- Demographics and other baseline characteristics;
- Medical history and concomitant diseases;
- Prior and concomitant therapies (medication, non-drug treatments, and procedures); and
- Extent of exposure.

Disposition of subjects, demographic data, and baseline characteristics will be presented using standard descriptive statistics. Demographic data will be summarized for SES, ITT, and PPS; remaining baseline data will be summarized descriptively only for the ITT and PPS.

13.5 Special Statistical/ Analytical Issues

13.5.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

13.5.3 CCI

CCI

[redacted]

14 ADMINISTRATIVE PROCEDURES

14.1 Study Monitoring

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

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

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

Investigators agree to grant access to all relevant documents and provide support at all times for study monitoring activities. Study monitoring 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 set forth in the monitoring manual.

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), and by this, if on-site visits are not possible due to site closures, travel limitations, or other considerations (e.g., if site personnel or trial subjects become infected with SARS-CoV-2), the following mitigations should be considered and assessed in an updated monitoring plan:

- On-site monitoring visits might be cancelled and/or the period between monitoring visits extended. When planned on-site monitoring visits are not possible, the reason should be clearly documented and made available for review during audits and/or inspections.
- Phone and/or video visits will be implemented when feasible, considering site closures, reduced staff, and any other circumstances.
- Remote monitoring or central monitoring could substitute on-site monitoring, when technically feasible.
- Protocol deviations will be tracked and documented if deviations occurred due to the public health emergency.
- Current local regulations, including data privacy regulations, will be considered when accessing source data remotely.

14.2 Data Quality Assurance

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

14.2.1 Standardization Procedures

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). Standardized photography methods will be detailed in a separate photography user manual.

This study will be monitored regularly by a qualified monitor from the CRO according to GCP guidelines and the respective standard operating procedures (SOPs; see Section 14.1).

14.2.2 Data Management

Data required according to this protocol are to be recorded in the web-based eCRFs provided by a CRO. All users who will enter data into the eCRF must successfully complete training before system access is granted. Participant training will be documented. Access to the eCRF will be password controlled and will conform with 21 CFR Part 11.

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 study 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 study personnel can be raised during source data verification and/or during medical, safety, and/or data management review.

Photographs will be archived by the central photography vendor in a system separate from the database (see Section 14.3). eDiary data will be transferred electronically to the data management CRO. Checks will be performed to ensure plausibility and completeness of these data. The data management activities and photographs processing will be delegated to the CROs listed in CCI [redacted] For analysis of the main period, the database of the main period will be closed after all data of the main period are entered and all queries concerning these data are solved. For the analysis at the end of the safety follow-up period, after all data from the safety follow-up period are entered and all queries are solved, the database close (including main and safety follow-up periods) will be performed. If any data changes are required after database close, these changes will be documented according to the respective SOP.

Further details of the data management process will be described in the data management plan.

14.2.3 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 CSP and that reliable and complete data have been entered into the eCRF.

All data required by this CSP 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.

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

If corrections are necessary, an authorized member of the investigator's study 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 study 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.

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), and by this, if data entry and cleaning is limited or not possible due to site closures, travel limitations, or other considerations (e.g., if site personnel become infected with SARS-CoV-2), the following mitigations should be considered for data cleaning processes:

- Data entry and response to data clarifications will proceed depending on availability of study site personnel and investigators.
- Depending on the content of the response to data clarifications, the need for source data review will be assessed by the sponsor.
- If applicable, a risk-based assessment for closing long opened data clarifications will be applied considering their impact on trial conclusion and data validity.
- The need for data clarifications and/or eCRF pages to be signed by staff that is not yet on the delegation log will be assessed. The delegation log is to be updated, if applicable.

14.2.4 Auditing

To ensure compliance with applicable standards and regulations, the sponsor, IEC/IRB, or regulatory authorities may conduct a quality assurance assessment or audit of site records at any time during or after completion of the study. In the event of an audit, investigators must grant access to all relevant documents (including source documents, electronic records, and other applicable study documentation) and provide support at all times for auditing activities.

14.3 Record Retention

Essential documents should be retained per applicable regulations and as instructed by the study sponsor. Essential documents at the investigational 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 study protocol 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;
- CCI [redacted]
- Copies of IMD receipt forms and device inventory forms; and
- Copies of safety information reported during the investigation and submitted by the sponsor.

Study documents may not be destroyed by study-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 study, the investigator must maintain all study-site records in a safe and secure location. The investigator is responsible for the integrity, retention, and security of all study-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 such a way as 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 study records to ensure that suitable arrangements for the retention of study records are made.

14.4 Publication Policy

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

The CSP, study data, and information related the study 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 study may be used for submission to national or international registration and supervising authorities. The sponsor may disclose the information obtained during the study to regulatory authorities or other personnel as required. If necessary, the sponsor may disclose the names, contact information, and qualifications of all investigators as well as their roles in the study. Upon completion of the study, publication or disclosure of the study results is to follow the terms contained in the sponsor's SOP.

The sponsor will ensure that a description of this clinical study is registered, and study results are disclosed on http://www.ClinicalTrials.gov, as required by U.S. law. Study registration may include a list of study sites, as applicable.

14.5 Financial Disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require sponsors to obtain certain financial information from investigators participating in covered clinical studies. By participating in the study, the investigator agrees to provide the required financial information and to promptly update the sponsor with any relevant changes to this financial information throughout the course of the study and for up to one year after its completion if necessary.

14.6 Investigator Compliance

The investigator will conduct the study in compliance with the protocol provided by the sponsor and in accordance with all relevant regulatory guidelines and requirements.

Modifications to the protocol should not be made without the agreement of the investigator and sponsor. The sponsor will submit all protocol modifications to the appropriate regulatory authority in accordance with applicable regulations. All protocol modifications require written IEC/IRB approval/favorable opinion, except in the case of an immediate hazard to subjects.

If an immediate deviation from the protocol is required to eliminate an immediate hazard to subjects, the investigator must contact the sponsor or assigned CRO, if possible, to

discuss the planned course of action. The investigator must thoroughly document any departure from the protocol and submit appropriate documentation to the sponsor without delay.

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