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Open-label, multicenter, uncontrolled, rater-blinded, post-market clinical follow-up [PMCF] study to confirm performance and safety of RADIESSE® (+) Lidocaine in the treatment of nasolabial folds, marionette lines, and/or cheek volume loss

Study identifier:	M900391005, RaLido
IDE number	Not applicable
Indications:	Nasolabial folds, marionette lines, and/or cheek volume loss
Planned study period:	First subject first visit: Q3 2018 Last primary outcome visit: Q2 2020 Last subject last visit: Q2 2020
Medical device:	RADIESSE® (+) Lidocaine
Sponsor:	Merz Pharmaceuticals GmbH Eckenheimer Landstraße 100 60318 Frankfurt am Main Telephone: +49-69-1503-0 Telefax: +49-69-1503-200
Responsible for the clinical protocol content at the sponsor:	Clinical project manager: [redacted] Medical expert: [redacted] Biostatistician: [redacted] Safety Officer: [redacted]
Clinical study sites:	15-20 sites in Germany
Statement:	This clinical protocol is defined in accordance with DIN EN ISO 14155:2012 / ICH GCP / MEDDEV 2.12/2 rev. 2- January 2012

SIGNATURE PAGE

The study will be conducted in compliance with the clinical protocol [CP], DIN EN ISO 14155:2012, the Declaration of Helsinki, and regulatory authority requirements.

The following individuals are responsible for the content of the CP:

[redacted]
Clinical project manager Date Signature

[redacted]
Medical expert Date Signature

[redacted]
Biostatistician Date Signature

[redacted]
Program Manager Date Signature

Statement of Compliance

Study Site(s)

I have thoroughly read and reviewed the CP. Having understood the requirements and conditions of the CP, I agree to perform the clinical study according to the CP, the electronic Case Report Form [eCRF], DIN EN ISO 14155:2012, the Declaration of Helsinki, and regulatory authority requirements.

I have received the current instructions for use [IFU 2017] leaflet and have been adequately informed about the study medical device [SMD] development to date, I also agree to:

- Sign this CP before the study formally starts.
- Wait until I have received approval from the appropriate ethics committee [EC] before enrolling any subject in this study.
- Obtain informed consent for all subjects prior to any study-related action performed.
- Start the study only after all legal requirements in my country have been fulfilled.
- Permit study-related monitoring, audits, EC review, and regulatory inspections.
- Provide direct access to all study-related records, source documents, and subject files for the monitor, auditor, EC, or regulatory authority upon request.
- Use the SMD and all study materials only as specified in the CP.
- Report to the responsible medical device safety officer, within 24 hours, any adverse event [AE] that is serious, whether considered treatment-related or not.

Furthermore, I understand that:

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

Principal investigator Date Signature

Print Name

Study site stamp:

List of Abbreviations and Definitions of Terms

AE	Adverse event
ADE	Adverse device effect
APAC	Asia Pacific
ASADE	Anticipated serious adverse device effect
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
CaHA	Calcium hydroxylapatite
CE	Conformité Européenne
CIP	Clinical Investigation Plan (term is synonymous with CP, Clinical Protocol)
CP	Clinical protocol
CRO	Contract research organization
eCRF	Electronic case report form
EC	Ethics committee
EU	European Union
FAS	Full analysis set
FDA	American Food and Drug Administration
GCP	Good clinical practice
HA	Hyaluronic acid
IFU	Instructions for use
iGAIS	Investigator Global Aesthetic Improvement Scale
IMD	Investigational Medical Device (term is synonymous with SMD, study medical device)
ISF	Investigator's site file
ISO	International Organization for Standardization
LATAM	Latin America
MAS	Merz Aesthetic Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMLS	Merz Marionette Lines Scale
MNLFS	Merz Nasolabial Folds Scale
MUCFS	Merz Upper Cheek Fullness Scale
N	Number of non-missing observations
PMCF	Post-market clinical follow-up

PPS	Per protocol set
SAE	Serious adverse event
SADE	Serious adverse device effect
SAP	Statistical analysis plan
SES	Safety evaluation set
sGAIS	Subject Global Aesthetic Improvement Scale
SMD	Study medical device
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
TC	Telephone contact
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
V	Visit
VAS	Visual analogue scale

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1 SYNOPSIS

Study title

Open-label, multicenter, uncontrolled, rater-blinded, post-market clinical follow-up [PMCF] study to confirm performance and safety of RADIESSE® (+) Lidocaine in the treatment of nasolabial folds, marionette lines, and/or cheek volume loss.

Indications

Nasolabial folds, marionette lines, and/or cheek volume loss.

Study objectives

Primary objective(s)

The primary objective of this post-market clinical follow-up study is to collect clinical data to confirm performance and safety for the injectable medical device RADIESSE® (+) Lidocaine, when used in accordance with its labelling in the treatment of nasolabial folds, marionette lines and/or cheek volume loss. The primary objective time point will be at Week 12/16 (depending on touch up).

Secondary objective(s)

The secondary objective is to analyse performance at all objective time point(s) other than the primary ones.

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

Main inclusion criteria:

1. Male or female ≥18 years old.
2. Subjects seeking for dermal filler/volumising treatment in at least two of the following indications:
    - Nasolabial folds;
    - Marionette lines;
    - Cheek volume loss.
3. Nasolabial folds volume deficit of moderate to very severe intensity (grade 2-4) on the Merz Nasolabial Folds Scale with symmetrical rating at Day 1 as determined by the blinded rater and confirmed by the treating investigator afterwards.

4. Marionette lines volume deficit of moderate to very severe intensity (grade 2-4) on the Merz Marionette Lines Scale with symmetrical rating at Day 1 as determined by the blinded rater and confirmed by the treating investigator afterwards.

5. Upper cheek volume deficit of moderate to very severe intensity (grade 2-4) on the Merz Upper Cheek Fullness Scale with symmetrical rating at Day 1 as determined by the blinded rater and confirmed by the treating investigator afterwards.

At least two of the inclusion criteria 3, 4, and 5 must be fulfilled. Depending on the fulfilled criteria, the respective indications will be treated.

Main exclusion criteria:

1. Any prior treatment with silicone, polymethyl methacrylate, fat injections, poly L-lactic acid or permanent dermal fillers in the face.
2. Any prior facial surgery, including facial plastic surgery, thread lift, any unknown treatment, or any surgical permanent implant that could interfere with performance assessments.
3. Prior treatment within the past 24 months with porcine based collagen fillers or with volumisers (e.g., Belotero® Volume or others) in the area to be treated.
4. Prior treatment within the past 18 months with calcium hydroxylapatite in the area to be treated.
5. Prior treatment within the past 12 months with hyaluronic acid in the area to be treated.
6. Prior treatment within the past 6 months with facial dermal therapies (e.g. epilation, ultraviolet irradiation, radiofrequency, facial ablative or non-ablative laser treatment, microderm abrasion, mechanical or chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage] or surgical procedures) or plans to receive this during participation in the study.

Medical device

RADIESSE® (+) Lidocaine is CE-marked in Europe since 02-JUN-2016. It is a sterile, non-pyrogenic, semi-solid, cohesive implant. The principle component is synthetic calcium hydroxylapatite suspended in a gel carrier that consists primarily of water (sterile water for injection USP), glycerin (USP), sodium carboxymethylcellulose (USP), and 0.3% lidocaine hydrochloride. The gel is dissipated in vivo and replaced with soft tissue growth, while the calcium hydroxylapatite remains at the site of injection. The lidocaine provides short-term local anesthetic effect. The result is long-term yet non-permanent restoration and augmentation.

RADIESSE® (+) Lidocaine has a calcium hydroxylapatite particle size range of 25-45 microns. It is indicated for plastic/reconstructive 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.

Study design

This study is an open-label multicenter post-market clinical follow-up study with rater-blinded[1] live evaluation. There will be no control group as the objective is to confirm safety and performance in "real-life".

RADIESSE® (+) Lidocaine will be injected as per its current approved labelling and investigator's usual practice at Day 1 with an optional touch up treatment after 4 weeks.

The subject will be injected at Day 1 with appropriate quantity for each area to be treated, using injection techniques based on investigator's judgement, skin condition, safety and subject's expectations. A minimum of two and a maximum of three indications (nasolabial folds, marionette lines, and/or upper cheeks) per subject can be treated. An optional touch-up can be performed after 4 weeks (Visit 2) in one or more indications treated at Day 1, to obtain an optimal aesthetic outcome.

An interim analysis report is planned on 6 months data (Week 24/28 respectively, depending on the touch-up).

Planned study period

First subject first visit: Q3 2018
Last primary outcome visit: Q2 2020
Last subject last visit: Q2 2020

Duration of treatment per subject

The duration of the study per subject will be approximately 18 months (in case of no touch-up performed at Visit 2) and 19 months (in case of touch-up at Visit 2).

Variables for analysis

The primary performance variables are:

- Responder rate for **nasolabial folds** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the Merz

[1] The blinded rater does not know which indications were treated. He/she performs the Merz Aesthetic Scales live ratings and is also involved into the Merz Aesthetic Scales ratings at subject inclusion.

Nasolabial Folds Scale. Response defined as improvement of ≥ 1 point in both folds (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

- Responder rate for **marionette lines** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the Merz Marionette Lines Scale. Response defined as improvement of ≥ 1 point in both marionette lines (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

- Responder rate for **cheek fullness** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the Merz Upper Cheek Fullness Scale. Response defined as improvement of ≥ 1 point in both cheeks (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

The primary safety variable is:

- The occurrence of treatment emergent adverse events.

The secondary performance variables are:

- Responder rate for **nasolabial folds** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the Merz Nasolabial Folds Scale prior to optional touch-up at Visit 2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for nasolabial folds defined as improvement of ≥ 1 point in both folds (left and right) compared to Day 1 pre-injection.

- Responder rate for **marionette lines** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the Merz Marionette Lines Scale prior to optional touch-up at Visit 2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for marionette lines defined as improvement of ≥ 1 point in both marionette lines (left and right) compared to Day 1 pre-injection.

- Responder rate for **cheek fullness** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the Merz Upper Cheek Fullness Scale prior to optional touch-up at Visit 2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for cheek fullness defined as improvement of ≥ 1 point in both cheeks (left and right) compared to Day 1 pre-injection.

- Treating investigator's evaluation of the global aesthetic improvement on the investigator Global Aesthetic Improvement Scale from Day 1 pre-injection photos to Visit 2 (Week 4) prior to optional touch-up, to Week 12/16, to Week 24/28, to Week 48/52, and to Week 72/76 (depending on touch-up performed).
- Subject's evaluation of the global aesthetic improvement on the subject Global Aesthetic Improvement Scale from Day 1 pre-injection photos to Visit 2 (Week 4) prior to optional touch-up, to Week 12/16, to Week 24/28, to Week 48/52, and to Week 72/76 (depending on touch-up performed).

Total number of subjects and number of countries

A total number of 210 subjects in one country (Germany).

Number of study sites

A total of 15-20 study sites.

Number of visits

Six visits (if no touch-up is performed), six visits plus one telephone contact (if touch-up is performed in all indications that were treated at Day 1), or seven visits plus one telephone contact (if partial [i.e. in at least one, but not in all indications that were treated at Day 1] touch-up treatment is performed) in total.

Medical device, dose, and route of administration

RADIESSE® (+) Lidocaine will be injected as per its current approved labelling and investigator's usual practice.

Volume to be injected, techniques of injections and depths of injections are at the investigator's discretion according to the area to be treated, as well as the subject's expectations. Overcorrection should be avoided. Investigators should use only the needles provided in the SMD packaging, however, investigators are allowed to use cannulas at their own choice instead of the supplied needles, if cannulas instead of needles are usually being used in their daily practice.

Statistical analysis methods

All performance analyses will be based primarily on the full analysis set and additionally, for the primary performance analyses, on the per protocol set. Statistical tests will be one-sided hypothesis tests for responder rates. The Bonferroni Holm alpha correction will be used for three statistical tests to adhere to the global significance level of 0.025. Continuous variables (values and changes from baseline) will be summarized by number of non-missing values, mean, standard deviation, median, quartiles, minimum and

maximum. For qualitative variables, absolute and percent frequencies (N, %) will be displayed.

Primary performance variables

Responder rates will be summarized as absolute and percent frequencies (N, %). The aim of primary performance analyses is to show that there are:

- significantly more than 60% of responders in treatment of nasolabial folds;
- significantly more than 60% of responders in treatment of marionette lines;
- significantly more than 60% of responders in treatment of cheek volume loss.

A confirmatory exact one-sample binomial test will be used to test probability of being a responder (p) is above 60% separately for each indication:

- $H_{0\ nasolabial\ folds}: p \leq 0.6$ *vs.* $H_{1\ nasolabial\ folds}: p > 0.6$
- $H_{0\ marionette\ lines}: p \leq 0.6$ *vs.* $H_{1\ marionette\ lines}: p > 0.6$
- $H_{0\ cheek\ volume\ loss}: p \leq 0.6$ *vs.* $H_{1\ cheek\ volume\ loss}: p > 0.6$

Secondary performance variable

No additional key secondary hypotheses will be tested under control of the global type I error level. All secondary variables will be analysed descriptively as follows: responder rates for nasolabial folds, for marionette lines, and for cheek fullness of the remaining visits will be summarized as frequency tables with absolute and percent frequencies (N, %). Investigator and subject Global Aesthetic Improvement Scales will be displayed using descriptive summary statistics for continuous variables and as frequency tables with absolute and percent frequencies (N, %). Subgroup analysis will be done per indication (subjects treated for nasolabial folds, for marionette lines, and for cheek volume loss).

Manufacturer of the medical device(s)

Merz North America, Inc.
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Franksville WI 53126 U.S.A.
Telephone: 844.469.6379
E-Mail: mymerzsolutions@merz.com
(Manufacturer of RADIESSE® [+] Lidocaine)

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Interleuvenlaan 40
3001 Leuven
Belgium

Tel.: +32 16 38 12 11
(Manufacturer of needles)

2 STUDY ADMINISTRATIVE STRUCTURE

2.1 Internal responsibilities

Name	Function	Address
Merz North America, Inc.,	Legal manufacturer of the device	4133 Courtney St., Suite 10 Franksville, WI 53126, U.S.A. Telephone: +1 844 469 6379
Merz Pharmaceuticals GmbH	Sponsor	Eckenheimer Landstraße 100 60318 Frankfurt am Main Telephone: +49-69-1503-0
[redacted]	Clinical project manager	Telephone: [redacted] Telefax: [redacted] Email: [redacted]
[redacted]	Medical expert	Telephone: [redacted] Telefax: [redacted] Email: [redacted]
[redacted]	Biostatistician	Telephone: [redacted] Telefax: [redacted] Email: [redacted]
[redacted]	Medical device safety officer	Telephone: [redacted] Telefax: [redacted] Email: [redacted]

2.2 External responsibilities

The administrative structure for external responsibilities includes, but is not limited to, the following participants:

Name	Function	Address
[redacted]	CRO for clinical conduct	[redacted] Germany Telephone: [redacted] Telefax: [redacted] Email: [redacted]
[redacted]	CRO for data management and biostatistics	[redacted] Germany Telephone: [redacted] Telefax: [redacted] Email: [redacted]

For this study, the sponsor will maintain a list of all principal investigators.

3 ETHICS

3.1 Ethics committee

The following documents must be submitted to the responsible EC and approval should be obtained:

- The CP.
- Any amendment to the CP that is not solely of an administrative nature.
- The IFU and all updates.
- Subject information and informed consent forms, as well as updates (if applicable).
- All subject recruitment procedures and any advertisement used to recruit subjects (if applicable).
- Any other required documents.

If applicable, and in accordance with local legal requirements, the above documents also may be submitted to the respective regulatory authority(ies) for separate approval.

3.2 Ethical conduct of the study

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with DIN EN ISO 14155:2012/MEDDEV 2.12/2 rev. 2 – January 2012/ICH-GCP and applicable regulatory requirements.

3.3 Subject information and informed consent

3.3.1 Subject information

Prior to study enrollment, the subject will be given full verbal and written information on the nature, objective, significance, potential benefits, potential risks, alternative therapy, confidentiality, compensation, the right to question and terminate participation, and expected consequences of the study. This verbal and written information will be provided by the investigator (or authorized designee) according to the provisions set forth in the Declaration of Helsinki, ICH GCP, DIN EN ISO 14155:2012 (chap. 4.7), and MEDDEV 2.12/2 rev. 2 – January 2012. The obligations of the investigator are set forth in the CP, DIN EN ISO 14155:2012, and the respective national regulations governing medical research and experimentation on humans.

Each subject will have the opportunity to question the investigator (or authorized designee) about the study prior to giving consent.

3.3.2 Informed consent

Informed consent will be obtained in accordance with DIN EN ISO 14155:2012 (chap. 4.7) in writing directly from the subject.

The consent must be confirmed by the investigator (or authorized designee) who conducted the informed consent process. The informed consent process must be traceable from the available documentation. At a minimum, this documentation should include information regarding when the subject was first informed about the study and who supplied the information. The subject will be given a copy of the signed and dated written informed consent form as well as all consent form updates (if applicable).

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

3.3.3 Subject card

This is not applicable for the current study.

3.3.4 Subject privacy

The subject will be informed of procedures that protect the subject privacy. Although recorded data will be passed on in a coded manner to authorized individuals only, re-identification by the investigator (e.g., in case of emergencies) will be possible using the subject number assigned to the subject. Access to non-coded data will be allowed solely to check validity, and such access will be limited strictly to authorized individuals (e.g., the sponsor or individuals authorized by the sponsor, auditors, regulatory authorities, or members of ECs who have been bound to confidentiality. If the results of the study are published, the subject's identity will remain confidential.

Photographs will be used by the site staff only for support of evaluations and will not be published or otherwise disclosed.

3.4 Insurance

From the beginning of the study until its termination, each subject is insured against any health impairment occurring as a result of participation in the study, in accordance with German laws and regulations.

The subject will be informed by the investigator and through the subject's informed consent form about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the subject, if requested. Any medical deviation from the CP that is deemed to have occurred through the subject's own fault is not covered by this insurance.

The sponsor is usually not liable for injuries/cases of death that occur solely as a consequence of the subject's underlying disease or condition, or from diagnostic or therapeutic measures not specifically required by the agreed CP. The sponsor is also usually not liable for events resulting from negligence of the investigator, clinical study staff, including failure to act according to DIN EN ISO 14155:2012 or to comply strictly with the agreed CP.

3.5 Financing

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

4 INTRODUCTION

4.1 Study background

Facial aging

Facial aging is the result of innate (chronological) aging and external (e.g., sun-induced) damage that share the loss of normal elastic fiber functions and the loss of hyaluronic acid [HA] as key common features. Innate aging comprises the atrophy and sagging of facial fat compartments and the remodeling of the underlying bone, manifested by flattening or indentation of normally convex contours [Fitzgerald 2014, Truswell 2013] . Tissue ptosis and/or atrophy and are most commonly seen in the mid to lower face. The aging process differs between individuals and depends on genetic predisposition, on exposure to ultra-violet [UV] radiation, deleterious environmental factors, and nicotine and alcohol consumption [Thurstan 2012].

Soft tissue augmentation

Soft tissue augmentation with dermal fillers is a popular, minimally invasive aesthetic procedure to counteract the signs of aging [Carruthers 2009]. Unwanted wrinkles can be corrected by a variety of methods depending on their nature and causation. To select a suitable method, it is necessary to accurately define the wrinkles (depth, classification into dynamic folds, gravity-induced folds etc.) and evaluate the facial fat distribution.

Facial anatomy is complex since the three-dimensional aspect of the face must be considered in relation to functional anatomical components. These components are in permanent motion and muscle contractions result in facial expression. The thickness, color, mobility and texture of facial skin are variable and the fat layer, which is located in subcutaneous tissue layers between the skin and muscles, also varies in thickness. Many signs of aging are due to the loss of subcutaneous fat and so the use of fillers can help to create a more youthful appearance, thereby reducing many signs of aging [Carruthers 2008b].

A very effective method of treating facial folds and volume loss is the augmentation procedure in which absorbable or non-absorbable filler materials of various types are implanted or injected. If permanent implants (non-absorbable silicone or substances containing polyacrylamide or acrylates) are used, the effect can only be reversed with difficulties. This means that all the adverse effects of permanent implants such as slippage, allergy induction and nodule formation either remain for years or the implants must be removed surgically.

Biodegradable substances that are currently used are the subject's own body fat (autologous fatty tissue), polylactic acid, calcium hydroxylapatite [CaHA], and HA

produced by biotechnology methods. In 2016, most non-surgical augmentation treatments performed with a dermal filler in the US used a product based on HA, followed by CaHA [ASAPS 2017].

RADIESSE® (+) Lidocaine

RADIESSE® (+) Lidocaine is Conformité Européenne [CE]-marked in Europe since 02-JUN-2016. It is a sterile, non-pyrogenic, semi-solid, cohesive implant. The principle component is synthetic CaHA suspended in a gel carrier that consists primarily of water (sterile water for injection USP), glycerin (USP), sodium carboxymethylcellulose (USP), and 0.3% lidocaine hydrochloride. Itis formulated to augment volume and, subsequently, to stimulate collagen production [Marmur 2004]. It consists 30% of CaHA microspheres and 70% of sodium carboxymethylcellulose gel. The microspheres are composed of a synthetic form of a natural substance found in the bones and teeth with a particle size range of 25-45 microns. Carboxymethylcellulose is a derivative of cellulose and acetic acid. The substance is frequently applied as a thickening agent and stabilizer of emulsions in certain foods and nonfood products, and to increase the viscosity in liquid pharmacological preparations. After injection, the carboxymethylcellulose gel is rapidly broken down while CaHA microspheres act as a sort of platform for newly synthesized collagen. This means that the filler is slowly replaced by autologous connective tissue [Kadouch 2017].

As a deep dermal to subdermal implant, RADIESSE® (+) Lidocaine it is indicated for plastic and reconstructive surgery of the facial area, including the correction of moderate to severe facial wrinkles and folds, and restoration and/or correction of the signs of facial fat loss [Jacovella 2008]. The formulation without lidocaine has already received CE-certification in 2003 and was approved by the American Food and Drug Administration [FDA] in 2006. Since then, it has been investigated in many studies in different indications, demonstrating high effectiveness, subject satisfaction and a favorable safety profile [Kadouch 2017]. The new formulation with lidocaine was introduced in 2016 to enhance patient comfort during treatment [Schachter 2016].

The SMD used in this clinical study is a CE-marked dermal filler and approved for the indications that will be treated (see current version of the [IFU 2017]).

4.2 Study rationale

Essential features of safe and effective dermal fillers include facility of use, longevity of results, and minimization of adverse effects.

The purpose of this PMCF study is to collect clinical data on RADIESSE® (+) Lidocaine when used simultaneously in multiple indications and in accordance with the approved labelling, to confirm its clinical performance and safety, and to detect potential emerging risks based on factual evidence.

Current available scientific data, clinical data, and post-marketing surveillance data of the SMD itself and its version without lidocaine support and demonstrate the clinical performance and safety of the product when injected as per its IFU (see current version of [IFU 2017]) [Bass 2010, Graivier 2007, Jacovella 2008, Pavicic 2013, Tzikas 2008]. Although it is common practice to inject more than one indication in one treatment session (holistic approach), only few clinical data following combination treatment of more than one indication at the same time are available so far. It is therefore desirable that post-market clinical data of good quality is generated to investigate the safety and performance of the SMD when used according to its current IFU.

4.3 Risk analysis and risk-benefit assessment

Benefits

- CaHA is a biodegradable material [Pavicic 2015]; undesirable effects such as overcorrection of the treated area or dissatisfaction with the outcome of the corrective procedure subside spontaneously after a few months.
- AEs seen in clinical trials with CaHA were generally expected, mild in nature, and short in duration [Kadouch 2017, Rayess 2017, Sadick 2007]. Long-term follow-up studies showed the favorable safety profile of CaHA with mostly injection-related mild side-effects [Bass 2010].
- Allergies and immunological reactions due to CaHA occur very rarely compared to permanent filler materials [Kadouch 2017, Rayess 2017, Sadick 2007]. The risk to develop an allergic reaction to lidocaine is also considered low [Fathi 2016].
- The addition of lidocaine to CaHA provides better patient comfort during treatment [Schachter 2016].
- CaHA has some additional benefits over HA fillers such as longer lasting results and enhanced cellular end extracellular matrix proliferation [Yutskovskaya 2014, Zerbinati 2018].
- Treatment with CaHA provides a high long-term patient satisfaction [Fakhre 2009].
- Treatment with injectable devices is performed on an ambulatory basis. No special preparations for the procedure are required.
- Injection with CaHA is less invasive and less permanent than available invasive treatment options via plastic surgery.

The SMD is CE-marked in Europe and approved in US and several LATAM- and APAC countries.Risks:

In occasional cases, one or more of the events described below may occur either immediately or as a delayed reaction:

- For any implant material, possible adverse reactions that may occur include, but are not limited to, the following: inflammation, infection, fistula formation, extrusion, hematoma/ecchymosis, seroma, induration formation, inadequate healing, skin discoloration/blanching of the skin, inadequate or excessive augmentation, contour irregularity, lumps, granulomas, hardening of the tissue at the injection site. Irregularity of the implant may require a surgical procedure to correct. In extreme cases, overcorrection can lead to site rupture. Overcorrection is not allowed in this study.
- An important untoward occurrence for any implant material is the introduction of the product into the blood vessels, which may lead to embolization, occlusion of the vessels (vascular compromise), ischemia, or infarction which can lead to necrosis, cerebral ischemia or cerebral hemorrhage, leading to stroke, and damage to underlying facial structures. In rare cases, such embolization can lead to blindness, especially when the dorsum of the nose is treated [Rayess 2017]. In this study, nose correction is not allowed and only well trained and experienced physicians with a deep knowledge of the facial anatomy will be included in this study. The investigator is advised to take extra care during the procedure. He/she needs to inject the SMD slowly and apply the least amount of pressure necessary. If some subject exhibits symptoms of blanching of the skin or unusual pain during or shortly after the procedure, subjects should receive prompt medical attention and evaluation by an appropriate health care practitioner specialist.

Adverse Events recorded in the studies with RADIESSE® (+) Lidocaine

- Adverse events seen in a clinical trial with RADIESSE® (+) Lidocaine injectable implant were generally expected, mild in nature, and short in duration. In a multi-center, randomized, controlled trial for the treatment of nasolabial folds by subdermal injection, one fold was injected with the RADIESSE® injectable implant and the other fold was injected with the RADIESSE® (+) Lidocaine injectable implant. The most common adverse events reported were swelling and redness. There was no significant difference in adverse event rates between the nasolabial folds injected with RADIESSE® and those injected with RADIESSE® (+) Lidocaine. Needle jams occurred during RADIESSE® (+) Lidocaine injections in three (3/101, 3%) subjects. In all cases, the needle was replaced and the RADIESSE® (+) Lidocaine injections were completed without further sequelae. Of 13 blanching events described, one was associated with a vascular compromise event. There were two (2/102, 2%) vascular compromises that occurred in nasolabial folds injected with RADIESSE® and none that occurred in nasolabial folds injected with RADIESSE® (+) Lidocaine. Both occurrences of vascular compromise were treated and resolved. The following adverse events were reported during clinical trials performed with the RADIESSE® injectable implant (without lidocaine): ecchymosis, edema, erythema, nodule, pain,

pruritus, soreness, tenderness, numbness, contour irregularity, lumps, irritation, rash, needle jamming, discoloration, hardness, headache, scab, tightness, blood shot eyes, black eye, abrasion, spot, nerve sensitivity, dry, burning sensation, warm, stretched, pimple, flushed, feverish, ear running, backed-up salivary gland, firmness, hearing loss, and puffiness.

Post market surveillance for equivalent product, RADIESSE®.

- The following adverse events have been identified during post-approval use of RADIESSE®. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to RADIESSE®. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to 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, 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, Bell's palsy.

The CaHA particles are radio-opaque and are clearly visible on computer tomogram scans and may be visible in standard, plain radiography. Subjects need to be informed of the radio-opaque nature of the SMD, so that they can inform their primary care health professionals and/or radiologists. In a radiographic study of 58 patients, there was no indication of RADIESSE® (without lidocaine) potentially masking abnormal tissues or was interpreted as tumors in computer tomogram scans [Carruthers 2008a].

During injection, needle/cannula jam can occur in rare cases that can make needle/cannula change necessary.

Subjects using anti-coagulant or thrombolytic substances like aspirin may have increased reactions of bruising hematomas, nodules or bleeding at the injection site. Special care should apply in subjects suffering from severe bleeding disorders [DeLorenzi 2014]. In accordance with RADIESSE® (+) Lidocaine IFU, subjects with bleeding disorders or receiving therapy with anti-coagulation, anti-platelet, or thrombolytic medications (e.g., warfarin, heparin, clopidogrel), anti-inflammatory drugs (e.g., aspirin), or other substances known to increase coagulation time from ten days before to three days post-injection with the SMD are excluded from this clinical study.

Since the product investigated in this study is biodegradable, regular follow-up treatment may be necessary if a visible enhancement effect (optimal cosmetic correction) continues to be desired.

Conclusion:

The SMD is marketed for aesthetic treatments in the target indications for several years across different countries worldwide. Since then it has already been used in a variety of subject populations. It is likely that this experience would have identified any rare complications or problems that may become apparent only after widespread device use.

Considering all risks and benefits of the SMD the potential benefits outweigh the potential risks. The risk/benefit ratio of the device is considered as acceptable when used on subjects according to the current manufacturer's IFU.

5 STUDY OBJECTIVES

Primary objective(s)

The primary objective of this PMCF study is to collect clinical data to confirm performance and safety for the injectable medical device RADIESSE® (+) Lidocaine, when used in accordance with its labelling in the treatment of nasolabial folds, marionette lines and/or cheek volume loss. The primary objective time point will be at Week 12/16 (depending on touch-up).

Secondary objective(s)

The secondary objective is to analyse performance at all objective time point(s) other than the primary ones.

6 STUDY PLAN

6.1 Overall study design

This study is an open-label multicenter PMCF study with rater-blinded[2] live evaluation. There will be no control group as the objective is to confirm safety and performance in "real-life". Approximately 175 subjects per indication seeking for dermal filler/volumising treatment in the face who agree to participate by signing the written informed consent form and who are fulfilling inclusion/exclusion criteria will be enrolled at approximately 15-20 sites. Since subjects must be treated for at least two and up to three indications, selected out of nasolabial folds, marionette lines and cheek volume loss, about 210 subjects in total are planned to be enrolled to collect data from about 175 subjects per separate indication (it is assumed that 50% of subjects will be treated for two and 50% for three indications, respectively).

At least 105 subjects will be treated in all of the three indications (i.e. nasolabial folds, marionette lines, and cheek volume). In addition, 35 subjects will be treated for each of the three treatment combinations:

- Nasolabial folds + marionette line;
- Nasolabial folds + cheek volume;
- Marionette lines + cheek volume.

If the number of subjects treated in all of the three indications is higher than 105, the number of the subjects treated for only two indications may be reduced so that the total number of all treated subjects will be 210.

The SMD is CE-marked in Europe since 02-JUN-2016 and will be injected as per its current approved labelling and investigator's usual practice at Day 1 with an optional touch-up treatment after 4 weeks.

The duration of the study per subject will be approximately 18 months (in case of no touch-up performed at Visit [V] 2) and 19 months (in case of touch-up performed at V2).

The subject will be injected at Day 1 with volume for each area to be treated, using injection techniques based on investigator's judgement, skin condition, safety and subject's expectations. A minimum of two and a maximum of three indications (nasolabial folds, marionette lines, cheeks) per subject can be treated. An optional touch-

[2] The blinded rater does not know which indications were treated. He/she performs the Merz Aesthetic Scales [MAS] live ratings and is also involved into the MAS ratings at subject inclusion.

up can be performed after four weeks at V2 in the indications that were treated at Day 1, to obtain an optimal aesthetic outcome, as appropriate.

If the subject fulfills the inclusion criteria and agrees to participate, he/she will attend six visits (if no touch-up is performed), six visits plus one telephone contact [TC] (if touch-up is performed in all indications that were treated at Day 1), or seven visits plus one TC (if partial [i.e. in at least one, but not in all indications that were treated at Day 1] touch-up treatment is performed) in total. If any serious AE [SAE] related to the injection or the SMD is not resolved by the end of the study, the subject will be followed until the resolution of the SAE by the Merz Pharmaceuticals Department of Product Safety.

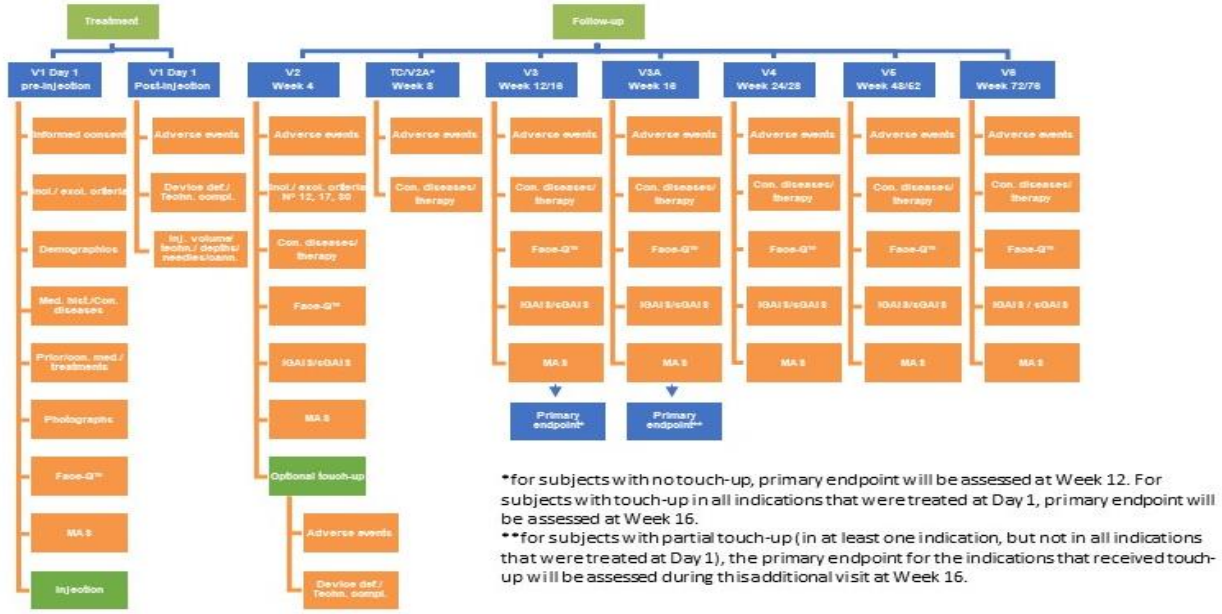
An interim analysis report is planned on 6 months data (Week 24/28 respectively, depending on touch-up).

6.1.1 End of study

The end of study will be defined as the last visit of the last subject.

6.1.2 Study flow chart

Figure 1: Study Flow Chart



6.2 Discussion of study design, including choice of control groups

The prospective, open label multicenter PMCF study design was chosen to adequately investigate the performance and safety of the SMD as per the current practice.

In general, prospective designs can achieve a higher data quality as compared to retrospective designs.

In order to collect "real-life" data, it has been decided not to interfere with investigators' usual practice and therefore employ a PMCF design. This design will allow evaluation of performance and safety of the SMD while used as per its current approved IFU.

Using several study sites increases the representativeness of the study results and decreases study site-related biases.

The observational period of approximately 18 to 19 months (if touch-up has been performed) was chosen to allow assessment of late-onset reactions.

The volume of the SMD to be injected as well as the choice of the injection technique are at the discretion of the investigator. This reflects the common use of fillers among physicians because the volume is adapted to the depths and the size of the areas to be treated as well as to the quality/thickness of the skin in these areas. Moreover, it depends on the desired cosmetic outcome which is usually a collective decision of both the treating physician and the subject.

Investigators should use only the needles provided in the SMD packaging, however, investigators are allowed to use cannulas at their own choice instead of the supplied needles, if cannulas instead of needles are usually being used in their daily practice. As this is a PMCF study with the main focus on performance and safety under real life conditions in daily practice, a control group that will be left untreated is not foreseen.

A blinded rater at each study site not otherwise involved in study procedures was chosen to assess the primary endpoint. The blinded rater does not know which indications were treated, which helps minimize the possible effects of evaluator bias.

7 STUDY POPULATION

7.1 Selection of study population

A total of approximately 210 adult subjects of both genders will be enrolled if they meet all of the inclusion and none of the exclusion criteria.

Investigators may recruit subjects from their existing pool of subjects, new subjects that are seeking facial aesthetic treatment, by word-of-mouth recommendation (e.g., satisfied subjects that formerly have received aesthetic treatment in the practice or clinic) or by advertisement.

Each of the three subpopulations, i.e. subject treated for nasolabial folds, marionette lines, and cheek volume loss, will contain approximately 175 subjects. Each subject will belong to at least two of these subpopulations. At least 50% of the subjects will be treated in all of the three indications and as consequence these subjects will belong to all of these three subpopulations (i.e. nasolabial folds, marionette lines, and cheek volume loss).

7.2 Inclusion criteria

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

Inclusion criteria	Rationale
1. Written informed consent obtained from the subject.	Administrative
2. Understanding of study procedures and willingness to abide by all procedures during the course of the study.	Administrative
3. Male or female ≥18 years old.	Administrative
4. Subjects seeking for dermal filler/volumising treatment in at least two of the following indications: o Nasolabial folds; o Marionette lines; o Cheek volume loss.	Performance

Inclusion criteria	Rationale
5. Nasolabial folds volume deficit of moderate to very severe intensity (grade 2-4) on the Merz Nasolabial Folds Scale [MNLFS] with symmetrical rating at Day 1 as determined by the blinded rater and confirmed by the treating investigator afterwards.	Performance
6. Marionette lines volume deficit of moderate to very severe intensity (grade 2-4) on the Merz Marionette Lines Scale [MMLS] with symmetrical rating at Day 1 as determined by the blinded rater and confirmed by the treating investigator afterwards.	Performance
7. Upper cheek volume deficit of moderate to very severe intensity (grade 2-4) on the Merz Upper Cheek Fullness Scale [MUCFS] with symmetrical rating at Day 1 as determined by the blinded rater and confirmed by the treating investigator afterwards.	Performance
8. Subject understands and accepts the obligation to follow study instructions and is logistically able to present for all scheduled study visits and meets all study requirements.	Administrative
9. Subject is willing to abide from all procedures (e.g., dermal fillers outside of this study, toxin treatments, facial ablative or fractional laser, microdermabrasion, chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage], and surgical procedures) in the face during participation in the study.	Safety concern
10. Subject will be compliant with contra-indications, precautions for use and warnings mentioned in the IFU of the injectable device to be injected (for details see exclusion criteria).	Safety concern
11. Women of childbearing potential[3] must be using a highly effective method of birth control.[4]	Safety concern

At least two of the inclusion criteria 5, 6, and 7 must be fulfilled depending on which indication will be treated.

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

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

7.3 Exclusion criteria

Subjects having any of the following criteria will not be included in the study:

Exclusion criteria	Rationale
1. Any prior treatment with silicone, polymethyl methacrylate, fat injections, poly L-lactic acid or permanent dermal fillers in the face.	Safety concern
2. Any prior facial surgery, including facial plastic surgery, thread lift, any unknown treatment, or any surgical permanent implant that could interfere with performance assessments.	Safety concern
3. Prior treatment within the past 24 months with porcine based collagen fillers or with volumisers (e.g., Belotero® Volume or others) in the area to be treated.	Safety concern
4. Prior treatment within the past 18 months with CaHA in the area to be treated.	Safety concern
5. Prior treatment within the past 12 months with HA in the area to be treated.	Safety concern
6. Prior treatment within the past 6 months with facial dermal therapies (e.g., epilation, UV irradiation, radiofrequency, facial ablative or non-ablative laser treatment, microdermal abrasion, mechanical or chemical peels, non-invasive skin-tightening [e.g., Ultherapy, Thermage], surgical procedures) or plans to receive this during participation in the study.	Safety concern
7. Prior treatment within the past 4 months with botulinum toxin in the area to be treated or plans to receive it during participation in the study.	Safety concern
8. Use of any new over-the-counter or prescription, oral or topical, anti-wrinkle products within 3 months prior to study inclusion or intention to use such products along the study duration. NOTE: Use of sunscreens and continued therapy with some cosmeceuticals, e.g., alpha hydroxyl acids, glycolic acids, skin-bleaching agents, retinol, or retinoic acids, are allowed if the regimen was established > 3 months prior to enrollment.	Safety concern
9. Prior treatment within the past 2 months with immunosuppressive medications or systemic steroids (except intranasal/inhaled steroids) or plans to receive them during participation in the study.	Safety concern

Exclusion criteria	Rationale
10. Prior cosmetic treatment (e.g., facials) within the past 30 days in the area to be treated or plans to receive it during participation in the study.	Safety concern
11. Prior oral surgery (e.g., orthodontia, extraction, implants) within the past 30 days or plans to undergo it during participation in the study.	Safety concern
12. Any known bleeding disorder, intake or planned intake of anti-coagulation, anti-platelet, or thrombolytic medications (e.g., aspirin, warfarin, heparin, clopidogrel), anti-inflammatory drugs (e.g., aspirin), or other substances known to increase coagulation time ten days prior and up to three days post SMD application.	Safety concern
13. Facial hair (e.g., beard) or other conditions (e.g., sideburns, etc.) that might interfere with study assessments.	Performance
14. Actinic damaged skin, premature aging skin, or poor vascularized tissue in the area to be treated.	Performance
15. History of allergic/anaphylactic reactions including hypersensitivity to lidocaine or anesthetics of the amide type, or any other components of the SMD.	Safety concern
16. Congenital methemoglobinemia, with glucose-6-phosphate dehydrogenase deficiencies, or concomitant treatment with methemoglobin-inducing agents.	Safety concern
17. Acute or chronic inflammation or infection at the injection site (e.g., acne).	Safety concern
18. History of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of AEs.	Safety concern
19. Tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads.	Safety concern
20. History of recurrent or chronic infraorbital edema.	Safety concern
21. Ectropium of the lower eyelid or eye diseases that lead to reddening and tendency of watering of the eye.	Safety concern
22. Facial nerve palsy or history of facial nerve palsy.	Safety concern

Exclusion criteria	Rationale
23. Facial skin and/or lipoatrophy other than age-related, due to medical conditions (e.g., congenital defect, trauma), or abnormalities in adipose tissue related to immune-mediated diseases, such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons-Syndrome), inherited disease or HIV-related disease.	Safety concern
24. A propensity towards pigmentary skin changes such as hyper- or hypopigmentation in the face, inflammatory skin conditions, keloid formation, or hypertrophic scarring.	Safety concern
25. History or documented evidence of an autoimmune disease (e.g., scleroderma, lupus erythematosus, rheumatoid arthritis).	Safety concern
26. History of recurrent herpetic eruption in the facial region.	Safety concern
27. Systemic disorders which cause poor wound healing or will lead to tissue deterioration over the treated areas.	Safety concern
28. Present or uncontrolled malignant disease.	Safety concern
29. Any medical condition with the potential to interfere with the study or compromise subject safety, or increase the risk of AEs (e.g., epilepsy, impaired cardiac conditions, severely impaired hepatic function, severe renal dysfunction, porphyria, severe psychic, neurological or mental disease, current or history of drug or alcohol abuse, general infection).	Safety concern
30. Pregnant, breast-feeding women, or women who are of childbearing potential and not practicing a reliable method of birth control.	Safety concern
31. Subject who is imprisoned or is lawfully kept in an institution.	Administrative
32. Employee or direct relative of an employee of the CRO, the study site, or Merz.	Administrative
33. Participation in a clinical study within the last 4 weeks prior to Day 1 and in parallel to this investigation.	Administrative
34. Previous participation in this clinical study.	Administrative

Exclusion criteria 12, 17, and 30 must be confirmed at V2 if touch-up treatment is planned.

In case that any of the exclusion criteria, e.g., history or presence of a disease, disorder, allergy, etc. might be unknown or questionable, the subject should not be included in the study until the respective exclusion criterion has been clarified.

7.4 Removal of subjects from treatment or assessment

7.4.1 Discontinuation of subjects

In accordance with the Declaration of Helsinki and the informed consent form, the subject may discontinue the study at any time without any penalty or loss of benefits to which the subject is otherwise entitled (see Section 7.4.3). Both the discontinuation of study and the reason(s) why the study was prematurely discontinued must be recorded in the subject file and the eCRF. Date and discontinuation circumstances should be stated.

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

- Withdrawal of informed consent.
- Pregnancy (no further administration of SMD will be performed).
- Any AEs for which treatment continuation would constitute an unacceptably high risk for the subject.
- Subject is lost to follow-up.

Clinical protocol deviations or conditions arising from the exclusion criteria established in Section 7.3, may (but will not necessarily) lead to the subject's discontinuation. All such conditions should be properly documented.

Subjects who are discontinued from the study due to AEs will be treated according to standard clinical strategies and will be followed-up until the final study visit/safety visit as described in Section 10. All pertinent information concerning the AE will be documented in the subject file as well as in the eCRF AE report form.

In case of study discontinuation of a subject the final study visit according to Table 7 should be performed for safety reasons. The investigator is required to make every effort to contact subjects lost to follow-up, and all such efforts should be documented in the subject file (e.g., times and dates of TC, copies of letters). Discontinued subjects will not be replaced.

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

The study or a study site can be prematurely terminated or suspended by the sponsor. Reasons for termination of the study or a study site may include, but are not limited to, the following:

- Subject enrollment is unsatisfactory.
- The risks and benefits of continuing the study have been reassessed, and the risks outweigh any potential benefits.
- In particular if an increase in the frequency or severity of expected AEs or newly identified harms, currently not regarded in the risk analysis, according to ISO 14971:2012 could have a significant impact on the benefit-risk analysis and which may lead to risks to the health or safety of subjects, users or other persons that are unacceptable when weighed against the intended benefits.
- New scientific data on the SMD do not justify a continuation of the study.
- The investigator or study site exhibit serious and/or persistent non-adherence to the CP, the Declaration of Helsinki, DIN EN ISO 14155:2012, and/or applicable regulatory requirements.
- The sponsor decides to terminate the study at any time for any other reason.

Furthermore, the study may be prematurely ended if the regulatory authority or the EC has decided to terminate or suspend approval for the study, the study site, or the investigator.

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

7.4.3 Provision of care for subjects after study discontinuation

After study discontinuation, the subjects will be treated by their physician according to their medical condition and standard treatments.

8 TREATMENTS

8.1 Study medical device

The SMD RADIESSE® (+) Lidocaine is CE-marked in Europe since 02-JUN-2016 and will be injected as per its current approved labelling and investigator's usual practice.

8.1.1 Description of study medical device

RADIESSE® (+) Lidocaine is a sterile, non-pyrogenic, semi-solid, cohesive implant. The principle component is synthetic CaHA suspended in a gel carrier that consists primarily of water (sterile water for injection USP), glycerin (USP), sodium carboxymethylcellulose (USP), and 0.3% lidocaine hydrochloride. The gel is dissipated in vivo and replaced with soft tissue growth, while the CaHA remains at the site of injection. The lidocaine provides short-term local anesthetic effect. The result is long-term yet non-permanent restoration and augmentation.

RADIESSE® (+) Lidocaine has a CaHA particle size range of 25-45 microns. It is indicated for plastic/reconstructive 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.

The SMD is provided sterile and non-pyrogenic in a syringe packaged in a foil pouch and boxed for convenient storage. Each syringe only unit consists of one pre-filled syringe containing 1.5 ml of RADIESSE® (+) Lidocaine and a Terumo K-Pack II with two 27 gauge thin wall injection needles.

8.1.1.1 Instructions for preparation

The instructions for preparation of RADIESSE® (+) Lidocaine (e.g., the correct assembling of the needle to the syringe) are to be followed as described in the current version of the IFU. The treating investigator should check the integrity of the inner packaging and the expiry date for both the syringes and the needles prior to use. The products must not be used if the expiry date has lapsed or if the packaging has been opened or damaged or if the syringe end cap or syringe plunger is not intact.

8.1.1.2 Instructions for administration

For successful treatment, it is essential that the treating investigator has experience with the injection techniques for treating nasolabial folds, marionette lines, and upper cheek

volume loss and has a deep knowledge of the facial anatomy. The treatment must be carried out under appropriate aseptic conditions.

The treating investigator determines the appropriate treatment area, depth, needle/cannula and injection technique based on clinical experience and preference in accordance with the current version of the IFU of the SMD. The SMD must be injected into a healthy, non-inflamed and previously rigorously disinfected skin. It should be injected into the deep dermal and/or subdermal soft tissue.

Injection volume of the SMD will be at the investigator's judgement based on subject's expectations, skin conditions and safety considerations and depends on the area to be treated and the extent of the volume loss/deficit. The optimal cosmetic outcome and an expected ≥ 1point improvement on the respective MAS in each treated area should be achieved. However, over-correction should be avoided.

The SMD should be injected slowly with the least amount of pressure necessary. It should not be injected into blood vessels, into areas presenting cutaneous problems of an inflammatory or infectious type (e.g., acne, herpes) or into an area previously treated with a permanent dermal filler. For full exclusion criteria, please refer to Section 7.3. Only the nasolabial folds, the marionette lines, and the upper cheek should be treated, other regions of the face must not be treated in this study.

If the needle/cannula becomes obstructed during the procedure and the injection pressure is too high, the treating investigator should stop the injection and change the needle/cannula.

After injection of SMD, the treated area can be gently massaged to distribute the product uniformly.

The investigator will use the SMD and all study materials only within the framework of the clinical study and in accordance with this CP.

8.1.2 Packaging and labelling

The packaging will be that of the commercialized products with additional labelling of "Studiennummer: M900391005", and „Medizinproduktenummer: XXXX" (SMD number with sequential numbering).

The SMD will be provided directly to each study site. If necessary during the course of the study, the study sites will be replenished with further study material.

8.1.3 Storage of study medical device

Storage of the SMD should be in accordance with the instruction leaflet (see current version of the [IFU 2017]).

8.1.4 Accountability for study medical device

It is the responsibility of the investigator to ensure that a current record of inventory accountability per site and per study subject is maintained. Inventory records must be readily available for the study monitor and are open to inspection by regulatory authorities at any time. Each shipment of materials for the study will contain an SMD supply and return form to assist the investigator in maintaining current and accurate inventory records. This form includes the following information: study number, dates, quantities, SMD number, and expiry date.

Upon receipt of the SMD, the investigator or his designated and authorized site staff will visually inspect the shipment and verify the number and condition of the SMD. The SMD supply and return form will be completed and signed by the investigator or authorized site staff. The completed form should be sent back to the sponsor, and the original signed form should be filed with the inventory accountability records.

To ensure proper storage and to verify inventory, a supply inspection will be conducted by the monitor. The results of the inspection will be made available to the authorized individuals (e.g., monitor, auditor, and regulatory authorities) on request throughout the study.

For subject device accountability and treatment compliance, see Section 8.2.5.

8.1.5 Destruction of study medical device

Upon the completion or termination of the study, all unused products will be returned to the sponsor. The sponsor will destroy the unused MD(s) after completion of the clinical investigation report. Destruction of MD(s) at the investigation site may be possible if written authorization is provided by the sponsor. If destruction at the investigation site is agreed upon, then a certificate of destruction must be given to the sponsor.

8.2 Treatments administered

The SMD will be applied according to the administration method and volumes described in the current IFU and in Section 8.2.2.

The treatment plan will consist of one injection session at Day 1 and an optional touch-up treatment after 4 weeks.

The following treatment order is recommended (depending on the indications the investigator considers for treatment):

- Progress from cranial to caudal (upper cheek augmentation before nasolabial folds and marionette lines).
- Nasolabial folds after upper cheek augmentation and before marionette lines.
- Marionette lines at the end.

8.2.1 Methods of assigning subjects to treatment groups

This is not applicable for the current study.

8.2.2 Selection of doses in the study

The volume to be injected is at the investigator's discretion according to the area to be treated as well as subject's expectations in order to achieve a desired improvement on the respective MAS in each treated area. Overcorrection must be avoided.

8.2.3 Selection and timing of doses for each subject

This is not applicable for the current study.

8.2.4 Duration of treatment per subject

The SMD will be injected at Day 1. An optional touch-up for one or more areas that were injected at Day 1 can be performed after 4 weeks +/- 7 days if deemed necessary by the investigator and the subject to achieve the optimal cosmetic correction.

8.2.5 Treatment compliance

At the beginning of the investigation, the site will receive device accountability forms to document how and when MD is dispensed to subjects, or returned unused. These forms

will be made available to the authorized individuals (e.g., monitor, auditor) and include the following information: study number, dates, quantities, and the SMD number assigned to the MD and study subjects.

8.2.6 Treatment of overdose

As treatment with SMD is performed exclusively in a clinical setting under the supervision of trained medical personnel, the risk of overdose in this study is estimated to be low. However, in the case an overdose occurred (i.e., over-correction), it must be recorded in the source documents and the SMD section of the eCRF and recorded as an AE. Any case of overdose leading to an SAE(s) must be reported to the sponsor in an expedited manner using the appropriate reporting form. Usually, overcorrection is an aesthetic issue and harmless for health. It resolves within 6 to 12 months without intervention.

The SMD, once implanted, cannot be easily removed, and a chirurgical intervention might be necessary in case of overcorrection.

8.3 Previous and concomitant therapies/procedures

After signature of the informed consent and prior to enrollment, the subject's previous and concomitant therapies and procedures should be reported in the eCRF. Previous and concomitant therapies/procedures should include a detailed list of all medications/non-drug therapies the subject was taking for a period of at least three months previous to Day 1. Facial treatments (such as surgery, aesthetic procedures) should be recorded regardless of time frame. For drug therapies, the record should include the drug name (trade or generic), route of administration (e.g., intravenous, oral), total daily dose and unit (expressed in mg, ml, or IU), indication, the start and stop date (day, month, and year), and whether the medication is ongoing at the end of the study. For non-drug therapies, the record should include the therapy name, body site and the start and stop date (day, month, and year).

Contra-indications and precautions for use mentioned in the SMD leaflet are to be checked prior to any injection and should be strictly respected.

Therapy changes (including changes of regimen) during the study are to be documented in the subject file and in the eCRF.

8.4 Blinding

A blinded rater who is not otherwise involved in any study procedures and who is not aware of the indications that will be treated will assess the primary and some of the other endpoints.

8.5 Restrictions during the study

The following restrictions to concomitant therapies will have to be observed during the study:

- No application of any new over-the-counter or prescription, oral or topical, anti-wrinkle products in the area to be treated during participation in this study.
- No cosmetic facial plastic surgery or oral surgery procedures (e.g., orthodontia, extraction, implants) during participation in the study.
- No dermal therapies (e.g., dermal fillers, toxin treatments, facial ablative or fractional laser, microdermabrasion, chemical peels, non-invasive skin-tightening, epilation, and surgical procedures) in the area to be treated during participation in the study.
- No immunosuppressive medications or systemic steroids region during participation in the study (except intranasal/inhaled steroids).
- No anti-coagulation, anti-platelet, or thrombolytic medications (e.g., aspirin, warfarin, heparin, clopidogrel), anti-inflammatory drugs (e.g., aspirin), from ten days before up to three days post SMD application.
- Use of sunscreens and continued therapy with some cosmeceuticals, e.g., alpha hydroxyl acids, glycolic acids, skin-bleaching agents, retinol, or retinoic acids, are allowed if the regimen was established > 3 months prior to enrollment.

The following actions and treatments are prohibited until the initial skin reddening/swelling has subsided:

- Application of makeup and touching/pressing of the treated parts of the face for at least 12 hours after treatment.
- Skin irritating agents (e.g., keratolytic, antiseborrheic, anti-acne agents) for at least three days after treatment in the treated area.
- Pigmenting and depigmenting agents for at least three days after treatment in the treated area.
- Promote facial rest for one week by encouraging subjects to limit talking, smiling and laughing.

- Extreme cold or heat (e.g., sauna, hot spring water, steam rooms) for at least 14 days after treatment.
- UV-exposure (sun or other UV ray emitters) for at least 14 days after treatment.

8.6 Precautions during and after the study

- The CaHA particles in the SMD are radio-opaque and are clearly visible on computer tomogram scans and may be visible in standard, plain radiography. Subjects need to be informed of the radio-opaque nature of the SMD, so that they can inform their primary care health professionals and/or radiologists.
- The investigator should council the subject to apply cool compresses to treated areas for approximately 24 hours.
- The investigator should council to massage the treatment area gently if palpable nodules become present.

9 STUDY ASSESSMENTS AND VISIT SCHEDULE

9.1 Clinical evaluations

At the beginning of the study, the subject's relevant medical history and all current and concomitant medications, treatments and procedures planned during the study as well as previous aesthetic procedures undertaken on the face will be recorded (see Section 8.3). A review of this information will allow the investigator to assess whether the subject should be enrolled. Treatment areas will be determined by the investigator. Other data will be collected as required, including complete information obtained from the examination of the treatment areas. If counseling of subjects is deemed necessary, either prior to enrollment or during the study, the investigator and/or subject might schedule an additional visit as necessary or clarify all issues during a planned study visit.

For time points of these assessments, please refer to Table 7.

9.2 Performance assessments

All assessments at a given study site should be performed by the same investigator for an individual subject enrolled at this site, if possible. A blinded rater, who is not otherwise involved in this study and who is also not aware of the treatment areas of the respective subject, will perform the MAS endpoint assessments by live rating. All assessments for an individual subject should be scored by the same blinded rater throughout the study, if possible. Subjects and the treating investigator will be instructed not to discuss the treatment areas with the blinded rater. The blinded rater must not have access to the subject`s file and the source data of the study.

It is strongly recommended that treating investigator and the blinded rater remain the same for each patient throughout the study, to ensure consistency in assessment.

Assessment collection time points are detailed in Table 7.

9.2.1 2D photographs

Three 2D photographs will be captured at baseline prior to SMD injection to serve as reference pictures for treating investigators and subjects for evaluation of iGAIS and sGAIS. The investigator will use his/her own photo equipment which he/she uses in daily practice. One full-face photograph from front view, and one full-face-photograph from 45° degree of each side per subjects should be taken with appropriate display of the

nasolabial folds, marionette lines, and upper cheek area. The subject should maintain a relaxed facial expression (no smiling, no grimacing).

9.2.2 *Merz Aesthetic Scales*

Clinical performance will be based on the assessment of the severity of nasolabial folds, marionette lines, and cheek volume on the published and validated 5point MAS [Carruthers 2012, Narins 2012]. Prior to study initiation, blinded rater(s) and treating investigator(s) at each site will be trained to perform the MAS assessments. At baseline the assessment is performed prior to SMD injection.

9.2.2.1 Merz Nasolabial Folds – At Rest Scale

The MNLFS (see Figure 2) will be used to assess the severity of nasolabial folds. The assessment will be performed separately for the left and the right nasolabial fold by the blinded rater and the treating investigator (baseline only) by live rating. For time points of this assessment, please refer to Table 7.

Figure 2: Merz Nasolabial Folds Scale

9.2.2.2 Merz Marionette Lines – At Rest Scale

The MMLS (see Figure 3) will be used to assess the severity of marionette lines. The assessment will be performed separately for the left and the right marionette line by the blinded rater and the treating investigator (baseline only) by live rating. For time points of this assessment, please refer to Table 7.

Figure 3: Merz Marionette Lines Scale

9.2.2.3 Merz Upper Cheek Fullness Scale – At Rest Scale

The MUCFS (see Figure 4 and 5) will be used to assess the severity of volume loss of upper cheeks. The assessment will be performed separately for the left and the right cheek by the blinded rater and the treating investigator (baseline only) by live rating. For time points of this assessment, please refer to Table 7.

Figure 4: Merz Upper Cheek Fullness Scale

Figure 5: Merz Upper Cheek Fullness Scale

9.2.3 Investigator Global Aesthetic Improvement Scale

The iGAIS (see Table 1) will be used to assess aesthetic improvement in the subjects. The assessment will be performed by the treating investigator by live rating using baseline photographs for comparison. For time points of this assessment, please refer to Table 7.

The treating investigator will be asked: “Based on your clinical experience, what is your overall impression of change of the subject´s aesthetic result due to treatment, compared to the condition before the first treatment (baseline)? Please check the one option that best fits your overall impression of change based on your comparison of the baseline visit photographs.”

Table 1: Investigator Global Aesthetic Improvement Scale

Score	Rating
+3	Very much improved
+2	Much improved
+1	Improved
0	No change
-1	Worse
-2	Much worse
-3	Very much worse

9.2.4 Subject Global Aesthetic Improvement Scale

The sGAIS (see Table 2) will be used to assess aesthetic improvement in the subjects. The assessment will be performed by the subject by live rating using baseline photographs for comparison. For time points of this assessment, please refer to Table 7.

The subject will be asked: "What is your overall impression of change of your aesthetic result due to treatment, compared to the condition before the injection? Please tick the one option that best fits your overall impression of change based on your comparison of the baseline visit photographs."

Table 2: Subject Global Aesthetic Improvement Scale

Score	Rating
+3	Very much improved
+2	Much improved
+1	Improved
0	No change
-1	Worse
-2	Much worse
-3	Very much worse

[redacted]

[redacted]

[redacted]

[redacted]

9.3 Safety assessments

Detailed information regarding the safety assessments is comprised in Section 10.

[redacted]

9.5 Visit schedule

The purpose of the baseline visit is to determine the subjects' eligibility for study participation. Subjects who are diagnosed with a medical condition during the screening process will be notified and referred for medical care. The screening evaluation must be completed prior to baseline.

Baseline is defined as V1/Day 1 (enrollment pre-injection), which is the day of injection of SMD in at least two out of three treatment regions (i.e., nasolabial folds, marionette lines, and/or cheek volume loss).

The study activities and the visit schedule are shown in Table 7. The study allows a time window of ±7 or ±14 days, depending on the visit. V6 (Week 72/76) is the final study visit.

If the subject meets the inclusion and exclusion criteria and agrees to participate, he/she will attend six or seven visits, depending on whether and in how many indications a touch-up treatment is done at V2 or not.

The primary endpoint for each treatment area will be evaluated 12 weeks after the last treatment, whether the last treatment occurred at V1 or as touch-up. Safety follow-up will occur up to 72/76 weeks post-treatment. Subjects who had the optional touch-up treatment will be contacted by telephone 4 weeks later and may have additional unscheduled visits if indicated by AEs or other safety issues. Unscheduled visits may be required in the case of premature discontinuation of the study. In this case, a final assessment will be performed. If additional safety follow-up is necessary after this assessment, subjects may be contacted by telephone or assessed in the practice/clinic, depending on the nature of the follow-up required.

Study Visits: **- V1/Injection visit (Day 1):** At this visit, the following procedures will be performed:

Before injection of SMD:

- Obtain written informed consent from the subject.
- Assessment of eligibility criteria.
- Assessment of demographic data (age, gender, race), previous and concomitant therapies, previous cosmetic procedures on the face, relevant medical history, and concomitant diseases.

- Based on the list of areas to be investigated, determination of subjects' face areas to be treated by the treating investigator (i.e., nasolabial folds, marionette lines, cheek volume loss) according to subjects' expectations.
- Assessment of baseline severity of each region according to the corresponding MAS by the blinded rater and the treating investigator.
- Full face photographs will be taken to have a comparison to later time points for global impression assessments.
- [redacted]
- Injection of the SMD as per its approved labelling (see current version of IFU) in a minimum of two treatment areas in order to achieve a ≥ 1point improvement on the respective MAS in each treated area.

After injection of SMD:

- [redacted]
- Assessment of AEs/SAEs/technical device deficiencies/complaints.

- V2/Follow-up visit with optional touch-up (Week 4 +/- 7 days): At this visit, the following procedures will be performed:

Before possible touch-up for area(s) injected at Day 1:

- Assessment of exclusion criteria N°12, 17, and 30.
- Assessment of concomitant medication/cosmetic procedures on the face and non-drug treatments.
- Assessment of AEs/SAEs/technical device deficiencies/complaints.
- [redacted]
- Assessment of iGAIS and sGAIS.
- Assessment of severity of each investigated region according to the corresponding MAS by the blinded rater.
- Injection of the SMD as per its approved labelling (see current version of IFU) (if touch-up is deemed necessary by the investigator and the subject) to achieve the optimal aesthetic correction.

After possible injection of SMD:

- [redacted]

- Assessment of AEs/SAEs/technical device deficiencies/complaints.
- Inform the subject that he/she will be called by phone for safety evaluation and concomitant diseases and therapies.

- V2A/Follow-up TC (Week 8 +/- 7 days; subjects with touch-up only):

Four weeks after the touch-up injections, all subjects that had a touch-up treatment in at least one region, will be called by phone for safety evaluation and concomitant diseases/therapies.

- V3/Follow-up visit/Primary endpoint visit (Week 12 /Week 16 +/- 7 days): If no touch-up was performed, V3 occurs at Week 12. Subject will come back to the site to evaluate performance and safety as well as to document investigator's and subject's global impression assessments. Follow-up visits will be performed further at Week 24, Week 48 and Week 72 (there will be no Week 16 visit for these subjects).

If touch-up was performed in at least one, but not in all indications treated at V1, V3 occurs at Week 12. Subject will come back to the site to evaluate performance and safety as well as to document investigator's and subject's global impression assessments. Additionally, subject performs V3a at Week 16. Follow-up visits will be performed further on Week 28, Week 52, Week 76.

If touch-up was performed at V2 in all indications treated at V1, V3 occurs at Week 16. Follow-up visits will be performed further at Week 28, Week 52, Week 76 (there will be no Week 12 visit for these subjects).

- Assessment of concomitant medication/cosmetic procedures on the face and non-drug treatments.
- Assessment of AEs/SAEs.
- [redacted]
- Assessment of iGAIS and sGAIS.
- Assessment of severity of each investigated region according to the corresponding MAS by the blinded rater.

- V3A/Follow-up visit/optional primary endpoint visit (Week 16 +/- 7 days):

This visit occurs in addition to V3, only if touch-up was performed at V2 for some but not all indications treated at V1. Sixteen weeks after the first injections at V1, the subject will come back to the site to evaluate performance and safety as well as to document

investigator's and subject's global impression assessments. This visit will serve as primary endpoint for the respective indication(s), i.e., nasolabial folds, marionette lines, or cheek volume loss, in which a touch-up was performed, provided that not all indications have been treated with touch-up. Follow-up visits will be performed further on at Week 28, Week 52, Week 76.

- Assessment of concomitant medication/cosmetic procedures on the face and non-drug treatments.
- Assessment of AEs/SAEs.
- [redacted]
- Assessment of iGAIS and sGAIS.
- Assessment of severity of each investigated region according to the corresponding MAS by the blinded rater.

- V4/Follow-up visit (Week 24/Week 28 +/- 14 days),

- V5/Follow-up visit (Week 48/Week 52 +/- 14 days), and

- V6/Follow-up visit/End of study visit (Week 72/Week 76 +/- 14 days): At these visits, the following procedures will be performed:

- Assessment of concomitant medication/cosmetic procedures on the face and non-drug treatments.
- Assessment of AEs/SAEs.
- [redacted]
- Assessment of iGAIS and sGAIS.
- Assessment of severity of each investigated region according to the corresponding MAS by the blinded rater.

Table 7: Overview of study activities/visit schedule

MRZ 900391005	Base-line	Follow-up/ **optional** touch-up	**TC** Follow-up	Prim. endpoint visit	**Optional** prim. endpoint visit	Follow-up visits	Final study visit[e]
Visit	V1	V2	V2A[b]	V3[c,d]	V3A[c]	V4[c,d] and 5[c,d]	V6[c,d,e] Final study visit
Timepoint	Day 1	Week 4	Week 8	Week 12/16	Week 16	Weeks 24/28 and 48/52	Week 72/76
Visit window		± 7 days	± 7 days	± 7 days	± 7 days	± 14 days	± 14 days
Informed consent	X						
Inclusion/exclusion criteria	X						
Exclusion criteria N° 12, 17, 30		X[b]					
Demographics	X						
Relevant medical history/concomitant diseases	X						
Previous & concomitant medications/treatm.	X	X	X	X	X	X	X
Photographs	X						
Determination of treatment indications	X	X[b]					
[redacted]							
iGAIS/sGAIS		X		X	X	X	X
MAS (blinded rater)	X[a]	X		X	X	X	X
MAS (treating invest.)	X[a]						
Injection/touch-up	X	X[b]					
[redacted]	[redacted]	[redacted]					
AEs /SAEs	X	X	X	X	X	X	X
Device deficiencies, technical complaints	X	X					

[a] MAS of blinded rater needs to be confirmed by the treating investigator prior SMD application;
[b] in case of optional touch-up;
[c] for subjects with no touch-up, primary endpoint will be assessed at Week 12. For subjects with touch-up in all indications treated at Day 1, primary endpoint will be assessed at Week 16. For patients with partial touch-up (in at least one indication, but not in all indications treated at Day 1), the primary endpoint for the indications that did not receive touch-up will be

assessed at Week 12 and for the indications that received touch-up will be assessed during the additional visit V3A at Week 16, follow-up visits will occur at Weeks 28, 52, and 76;

[d] if all indications treated at V1 are also treated at the optional touch-up, V3, 4, 5, and 6 will be at Weeks 16, 28, 52 and 76, respectively;

[e] in case of premature study discontinuation a final study visit has to be performed for the subject.

10 SAFETY ASSESSMENTS

10.1 Definition of an adverse event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1 This definition includes events related to the investigational medical device or the comparator.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

10.1.1 Adverse event details

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

AEs will not be followed up after the final visit, which is scheduled 72 or 76 weeks (depending on optional touch up) after first treatment with the SMD.

Treatment emergent adverse events (TEAEs) are defined as adverse events with onset or worsening at or after the first administration of study treatment.

Pre-existing conditions noted in the medical history and previous to SMD administration 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 condition of the subject at screening.

10.1.2 Adverse event handling and reporting

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

- AE diagnosis or main symptom.
- Location of AE: systemic or restricted to injection area. In case of local reaction, the corresponding area should be reported.
- Date of onset.
- Date of worsening.
- Severity (maximum observed; see Section 10.1.3).
- Causal relationship (not related, related).
- Serious (yes or no).
- Outcome (see Section 10.1.5).
- Action taken with SMD
- AE leading to discontinuation of the investigation (yes or no).
- Stop date.

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

In case of an serious adverse event (defined in section 10.2), the investigator must also complete an SAE report form and report it to the CRO immediately, as described in Section 10.2.2.

10.1.3 Adverse event severity grading scale

The clinical severity of an AE will be classified as:

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

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

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

The Investigator is required to grade the severity/intensity of each AE.

10.1.4 Causal relationship with medical device

An AE is considered to be "related" to SMD if a causal relationship between the SMD and an AE is at least reasonably possible (i.e., the relationship cannot be ruled out). In this case the event is considered an "adverse device effect" (see Section 10.3). If the event is serious (see above), it is a "serious adverse device effect"(see Section 10.4).

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."

10.1.5 Categories of outcome

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

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

10.2 Definition of a serious adverse event (SAE)

A SAE is an adverse event that:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect

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

10.2.1 Serious adverse event details

In case of a fatality, the cause of death is considered as the adverse event, and the death is considered as its outcome. In this case, the primary cause of death (the event leading to death) should be recorded and reported as an SAE. “Death” will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might be reported as an SAE. In case 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 as an SAE. If a subject experiences an additional AE that prolongs a pre-planned hospitalization, this is considered to be an SAE and should also be reported as an SAE. Hospitalizations for elective treatments planned before screening and which are documented in the subject’s source data are usually not regarded as SAEs.

Device deficiencies that might have led to an SAE if

a) suitable action had not been taken, or

b) intervention had not been made, or

c) if circumstances had been less fortunate

are handled under the SAE reporting system.

10.2.2 Reporting and handling of SAEs

All SAEs that occur during the investigation period, whether considered to be related to a SMD or not, must be reported via SAE report form to the CRO within 24 hours of knowledge of the event. The CRO will report the SAE to the sponsor. 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 (number).
- A suspect product and how the treatment relates to the SAE.
- An identifiable reporting source (investigator/investigation site identification).
- An event or outcome that can be identified as serious.

The report must be delivered to the individual(s) listed below.

The address for SAE reporting is:

[redacted]
Merz Pharmaceuticals GmbH
Global Product Safety Department
Eckenheimer Landstrasse 100
D – 60318 Frankfurt/Main
E-Mail: product.safety@merz.de in cc to MD-team@merz.de
Telephone: [redacted]
Fax: [redacted]
Mobile: [redacted]

The investigator must supply further supporting information within 3 days of knowledge of the SAE, and a detailed SAE description is an integral part of this supporting information. Follow-up reports should be sent without delay as an SAE report form (marked as a "follow-up" report) and accompanied by appropriate supporting documentation (e.g., hospital reports). The SAE has to be followed-up until the SAE is recovered/resolved 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.

SAEs occurring after the end of the observational period need only be reported if the investigator considers the event to be related to SMD.

As this study is considered as PMCF study based on §23b German "Medizinproduktegesetz", serious adverse device effects (see Section 10.4) need to be reported as incidents as well as near incidents by the sponsor accordingly based on the timelines defined in the current "Medizinproduktesicherheitsplanverordnung".

10.3 Definition of an adverse device effect (ADE)

An ADE is defined as an adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

10.4 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 (see Section 10.2).

10.4.1 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.

10.4.2 Definition of an unanticipated serious adverse device effect (USADE)

An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.5 Pregnancy

Each pregnancy that starts during the investigation must be reported by the investigator via Pregnancy report form within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on a pregnancy monitoring form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the SMD.

10.6 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 labelling.

10.6.1 Reporting and handling of device deficiencies

A device deficiency that could have led to a SADE (see Section 10.4) is to be reported in the same way as an SAE.

Device deficiencies must be reported to the following address:

[redacted]
Merz Pharma & Co. KGaA
Global Quality
Eckenheimer Landstrasse 100
D – 60318 Frankfurt/Main
E-Mail: complaints@merz.de in cc. to MD-team@merz.de
Telephone: [redacted]
Fax: [redacted]

The Global Quality department will decide if the concerned sample needs to be returned and to whom the product should be sent for investigation.

11 DATA QUALITY ASSURANCE

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

11.1 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, monitoring, centralized evaluations, and validation methods).

This study will be monitored regularly by a qualified monitor from the CRO according to DIN EN ISO 14155:2012, and the respective Standard Operating Procedures [SOPs] (see Section 11.4).

11.2 Source documentation requirements

All data collected from a subject during the course of a clinical study should be retained in the respective source documentation (e.g., subject file). The source documentation must also contain a descriptive statement on the informed consent procedure (see Section 3.3.2). The investigator must also confirm by written statement in the source documentation that all inclusion criteria and all exclusion criteria were checked prior to inclusion of the subject. In addition to this statement, the subject's meeting or non-meeting of the in- and exclusion criteria have to be traceable on the basis of the documentation in the subjects file. The childbearing potential of female subjects must be noted in the source documentation. Subjects, investigators and blinded raters' assessments must be filed in subject files. The site will keep a source data location list which will outline for the different data categories including electronic data (e.g., demographics, medical history, and AEs etc.) which document serves as source for this data (e.g., subject file and source data worksheet, if applicable).

If a study site is using an electronic system for documenting source data, a member of the site staff must print out the source data after each visit. The paper print-outs must be overlapping, if possible (i.e., must contain at least the last row of data from the subject's previous visit). If it is not possible to obtain overlapping paper print-outs, the completeness of source data must be ensured by other suitable means. The print-out must be signed and dated by a member of the site staff who can confirm the accuracy and

completeness of data in the paper print-out. The monitor should also sign and date after verifying the source data. The paper print-out should be stored in the Investigator's Site File [ISF] or in separate binders for the study. If source data information is entered retrospectively, this must be done directly on the paper print-out and should be initialed and dated. The same applies to any corrections of initial data.

If the site is using a validated computer system including audit trail with a separate access for the monitor (i.e., the monitor can only access the data of the study subjects), then no such paper print-outs are required.

11.3 Data management

Data required according to this protocol is to be recorded in the web-based eCRFs (electronic data capture system) provided by the CRO. All users who will enter data into the eCRF will be previously trained. After the successful completion of the training all participants will receive a training certificate, which will be a pre-requisite for the access to the eCRF. The access to the eCRF is password-controlled and conforms with the Code of Federal Regulations part 11.

Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data capture 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 site staff. The audit trail in the electronic data capture system documents 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 site staff) can be raised during source data verification, medical or safety review and data management review.

After all data up to Week 24/28 are entered and all queries are solved, the database will be closed for interim analysis (1st database close). Data will be exported and archived at SAS data sets. A second database close will take place after all remaining data have been entered and cleaned. Changes to data after 1st database close are documented exclusively in the audit trail of the electronic data capture system. The audit trail will be archived at the end of the study. In case of any changes to the data after 2nd database close, these changes will be documented according to respective SOP.

11.4 Monitoring

This study will be monitored regularly by a qualified monitor of the CRO according to DIN EN ISO 14155:2012 (chap. 8.2.4) and the respective SOPs. During these visits, the monitor will prepare the study site for the conduct of the study, check for subject

eligibility, for completion of the entries in the source data and on the eCRFs; for compliance with the CP, DIN EN ISO 14155:2012, the Declaration of Helsinki, and regulatory authority requirements; and for the integrity and verification of the source data with the eCRF entries. Monitoring also will be aimed at detecting any misconduct or fraud.

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

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

- Have all data properly recorded in the source documentation and the eCRF prior to each monitoring visit.
- Have the source documentation available at the monitoring visits.
- Record all units of SMD dispensed in the eCRF and the device inventory records.

All subjects who are screened, but not included into the study, will be listed on the subject enrollment log.

Further details of monitoring activities, if applicable, will be set forth in the monitoring plan.

11.5 Auditing

Audits will be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance function may arrange to visit the investigator in order to audit the performance of the study at the study site, as well as all study documents originating there. Auditors conduct their work independently of the observational study and its performance.

Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance function will agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the study site, the monitor will usually accompany the auditor(s).

In addition, standard routine quality control procedures will be employed according to the sponsor's SOPs.

12 STATISTICAL METHODS

This section describes the statistical analyses intended at the time of study planning. Further details on the statistical and analytical aspects will be presented in the statistical analysis plan [SAP].

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 CP or the SAP. All deviations and/or alterations will be summarized in the clinical study report.

12.1 Determination of sample size

The sample size estimation is based on the primary performance analyses, i.e., on three one-sided exact one-sample binomial tests (one test for each indication). Under the following assumptions 140 subjects are required per indication to reach a global power of 80%:

- Global significance level: 0.025 (one-sided)
- Local significance levels for tests per indication: α_1=0.0083, α_2=0.0125, α_3=0.025 (Bonferroni Holm adjusted alpha)
- Proportion of responders under the null hypothesis 0.6
- Expected responder rate under test treatment: 0.75
- Power for each single test: 89.6% (for α_1), 92.6% (for α_2), 96.6% (for α_3)
- Global power for all tests under independence 80.1%

In order to have sufficient subjects for safety analysis the sample size is increased to 175 subjects per indication so that a minimum of 161 subjects per indication will complete the study. In 161 subjects per indication an AE with a true incidence of 1% will be observed at least once per indication with a probability of 80%. The total number of 210 subjects to be treated was chosen to have approximately 175 subjects treated per indication.

12.2 Analysis sets

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

Safety Evaluation Set [SES]

The SES is the subset of all subjects who were exposed to the SMD at least once.

Full Analysis Set [FAS]

The FAS is the subset of subjects in the SES for whom at least one of the primary performance variables is available (i.e., all subjects who have a baseline and a post-baseline primary performance value of at least one treated indication).

Per Protocol Set [PPS]

The PPS is the subset of subjects in the FAS without major deviations. Major protocol deviations will be defined during the data review meeting.

12.3 Variables for analysis

12.3.1 Performance variables

12.3.1.1 Primary performance variable

The primary performance variables of this study are:

- Responder rate for **nasolabial folds** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MNLFS. Response defined as improvement of ≥ 1point in both folds (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).
    - V3 visit at Week 12 after first injection at Day 1, if no touch-up is done for nasolabial folds
    - V3 visit at Week 16 after first injection at Day 1, if a touch-up is done for nasolabial folds and for all further indications treated at V1
    - V3A visit at Week 16 after first injection at Day 1, if a touch-up is done for nasolabial folds, but not for all indications treated at V1
- Responder rate for **marionette lines** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MMLS. Response defined as improvement of ≥ 1point in both marionette lines (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).
    - V3 visit at Week 12 after first injection at Day 1, if no touch-up is done for marionette lines

- V3 visit at Week 16 after first injection at Day 1, if a touch-up is done for marionette lines and for all further indications treated at V1
- V3A visit at Week 16 after first injection at Day 1, if a touch-up is done for marionette lines, but not for all indications treated at V1

- Responder rate for **cheek fullness** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MUCFS. Response defined as improvement of ≥ 1point in both cheeks (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

  - V3 visit at Week 12 after first injection at Day 1, if no touch-up is done for cheek fullness
  - V3 visit at Week 16 after first injection at Day 1, if a touch-up is done for cheek fullness and for all further indications treated at V1
  - V3A visit at Week 16 after first injection at Day 1, if a touch-up is done for cheek fullness, but not for all indications treated at V1

Table 8 displays which visits will be used to for calculation of the primary variables depending on touch-up treatment.

Table 8: Visits to be used for calculation of the primary variables changes from baseline to primary follow up visit

		Baseline	Prim. endpoint visit	
Visit no.		1	3	3A
Timepoint		Day 1	Week 12/16	Week 16
Indication nasolabial folds	without touch-up	X	X	
	with touch-up in all indications	X	X	
	with touch-up for nasolabial folds, but not for all indications treated at V1	X		X
Indication marionette lines	without touch-up	X	X	
	with touch-up in all indications	X	X	
	with touch-up for marionette lines, but not for all indications treated at V1	X		X
Indication cheek fullness	without touch-up	X	X	
	with touch-up in all indications	X	X	
	with touch-up for cheek fullness, but not for all indications treated at V1	X		X

12.3.1.2 Secondary performance variables

Secondary performance variables are defined as follows:

- Responder rate for **nasolabial folds** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MNLFS prior to optional touch-up at V2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for nasolabial folds defined as improvement of ≥ 1point in both folds (left and right) compared to Day 1 pre-injection.

- Responder rate for **marionette lines** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MMLS prior to optional touch-up at V2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for marionette lines defined as improvement of ≥ 1point in both marionette lines (left and right) compared to Day 1 pre-injection.

- Responder rate for **cheek fullness** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MUCFS prior to optional touch-up at V2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for cheek fullness defined as improvement of ≥ 1point in both cheeks (left and right) compared to Day 1 pre-injection.

- Treating investigator's evaluation of the global aesthetic improvement on the iGAIS from Day 1 pre-injection photos to V2 (Week 4) prior to optional touch-up, to Week 12/16, to Week 24/28, to Week 48/52, and to Week 72/76 (depending on touch-up performed).
- Subject's evaluation of the global aesthetic improvement on the sGAIS from Day 1 pre-injection photos to V2 (Week 4) prior to optional touch-up, to Week 12/16, to Week 24/28, to Week 48/52, and to Week 72/76 (depending on touch-up performed).

[redacted]

[redacted]

12.3.2 Safety variables

12.3.2.1 Primary safety variable

The primary safety variable is:

- Occurrence of treatment emergent adverse events [TEAEs].

12.3.2.2 Secondary safety variables

Not applicable for the current study.

[redacted]

[redacted]

12.4 Statistical analysis methods

12.4.1 Performance variables

All performance analyses will be based primarily on the FAS and additionally for the primary performance analyses on the PPS. Where applicable subgroup analysis will be performed on the following subpopulation “nasolabial folds”, “marionette lines” and “cheek volume loss” (for details see section 12.4.4.5).

Statistical tests will be one-sided hypothesis tests for responder rates. The Bonferroni Holm alpha correction will be used for three statistical tests to adhere to the global significance level of 0.025. Continuous variables (values and changes from baseline) will be summarized by number of non-missing values, mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative variables, absolute and percent frequencies (N, %) will be displayed.

12.4.1.1 Primary performance variable

Responder rates for nasolabial folds, for cheek volume loss, and for marionette lines will be summarized as absolute and percent frequencies (N, %). Only the subjects of the FAS treated for the corresponding indication will be included into the analyses of responder rates (for details see section 12.4.4.5).

The aim of primary performance analyses is to show that there are:

- significantly more than 60% of responders in treatment of nasolabial folds
- significantly more than 60% of responders in treatment of marionette lines
- significantly more than 60% of responders in treatment of cheek volume loss

A confirmatory exact one-sample binomial test will be used to test probability of being a responder (p) is above 60% separately for each indication:

- $H_{0\ nasolabial\ folds}: p \leq 0.6$ vs. $H_{1\ nasolabial\ folds}: p > 0.6$

- $H_{0\ marionette\ lines}: p \leq 0.6$ *vs.* $H_{1\ marionette\ lines}: p > 0.6$
- $H_{0\ cheek\ volume\ loss}: p \leq 0.6$ *vs.* $H_{1\ cheek\ volume\ loss}: p > 0.6$

Using the Bonferroni Holm alpha correction with global significance level of 0.025 for the test with lowest p-value the local significance level α_1 is 0.0083. For the test with the second lowest p-value α_2 is 0.0125. For the test with the highest p-value α_3 is 0.025. If the lowest p-value of a single (one-sided) hypothesis is below 0.0083 it is shown that the responder rate lies significantly above 60% for this indication. In this case performance is shown for this indication. If additionally the second p-value of a single (one-sided) hypothesis is below 0.0125 it is shown that the responder rate lies significantly above 60% also for this indication. If additionally the highest p-values of the single sub-hypothesis are below 0.025, the primary objective regarding performance (i.e., performance shown for all three indications) can be concluded. The procedure is stopped if a p-value is higher than the corresponding local significance level. In this case no subsequent null hypothesis will be rejected.

Point estimates of the rates will be provided with exact one-sided 97.5% Clopper-Pearson confidence intervals.

12.4.1.2 Secondary performance variables

No additional key secondary hypotheses will be tested under control of the global type I error level. All secondary variables will be analysed descriptively as follows: Responder rates for nasolabial folds, for marionette lines, and for cheek fullness of the remaining visits will be summarized as frequency tables with absolute and percent frequencies (N, %). iGAIS and sGAIS will be displayed using descriptive summary statistics for continuous variables and as frequency tables with absolute and percent frequencies (N, %). Subgroup analysis for iGAIS and sGAIS will be done per indication (subjects treated for nasolabial folds, for marionette lines, and for cheek volume loss).

[redacted]

12.4.2 Safety variables

All safety analyses will be performed on the SES in total and by the subpopulations of each indication (subjects treated for nasolabial folds, for marionette lines, and for cheek volume loss). AEs will be coded according to the Medical Dictionary for Regulatory Activities [MedDRA] version in effect at the time the database is closed. Only TEAEs will be analysed which are defined as AEs with onset or worsening at or after the first administration of the SMD.

12.4.2.1 Primary safety variable

The main analysis for the primary safety variable will be the overall TEAE incidence rate(s). Further incidences will be calculated for TEAEs on the system organ class level and on the preferred term level (i.e., total, by intensity, and by relationship, by outcome, and by injection site area). Listings and, if applicable, tables displaying incidences for TEAEs leading to discontinuation, serious TEAEs, and deaths will also be provided.

12.4.2.2 Secondary safety variables

Not applicable for the current study.

[redacted]

[redacted]

12.4.4 Special statistical/analytical issues

12.4.4.1 Discontinuations and missing data

Discontinued subjects will not be replaced.

For responder analyses missing values will be evaluated as non-responder (worst case replacement). [redacted] analyses except responder analysis [redacted] will be performed on observed cases only.

12.4.4.2 Interim analyses

An interim analysis for the SES and the FAS will be performed including all data (safety, performance and other data) up to Week 24/28 respectively, depending on touch-up. The analyses of the subpopulations “nasolabial folds”, “marionette lines” and “cheek volume loss” is also part of the interim analysis (for details see section 12.4.4.5). The PPS analysis is not part of the interim analysis and will be done for the final analysis at the end of the study in addition to SES and FAS. A combined SAP containing interim analysis and end of study analysis will be written. Tables to be created for the interim analysis and data to be included will be described in detail in the SAP. The interim analysis will be done for obtaining the performance and safety data up to Week 24/28 as early as possible. Therefore, the purpose of this interim analysis is not to perform any adaptions on the study design, statistical analysis, sample size or for stopping the study, as this is not a study with an adaptive design.

Since this is an open label study, the interim analysis will not have any influence on the integrity of the study data and it will not bias the data collected after interim analysis.

12.4.4.3 Data monitoring committee

Not applicable for the current study.

12.4.4.4 Multiple comparisons/multiplicity

Three confirmatory tests will be performed in the primary analysis, one for each primary performance variable of the corresponding indication. Bonferroni Holm correction will be used to counteract the problem of multiple comparisons. For the three statistical test the local significance levels α_1=0.025/3, α_2=0.025/2 and α_3=0.025 will be applied to obtain the global significance level of 0.025.

12.4.4.5 Examination of subgroups

The subpopulation “nasolabial folds” will contain all subjects treated for nasolabial folds, regardless if they have been treated for one or both other indications as well. The subpopulation “marionette lines” will contain all subjects treated for marionette lines, regardless if they have been treated for only one or for two other indications as well. The subpopulation “cheek volume loss” will contain all subjects treated for cheek volume loss, regardless if they have been treated for one or both other indications as well. Each of these three subpopulations will contain approximately 175 subjects. Each subject will belong to at least two of these subpopulations. At least 50% of the subjects will be treated in all of the three indications and as consequence these subjects will belong to all of these three subpopulations (i.e., nasolabial folds, marionette lines, and cheek volume loss).

For the performance variables iGAIS, sGAIS, [redacted] for subject dispositions, demographic data, and for all safety analyses (analysis of TEAEs), subgroup analyses will be performed for each indication (subjects treated for nasolabial folds, for marionette lines and/or for cheek volume loss) in addition to the total population.

Responder analysis of MNLFS, MUCFS, and MMLS will only be performed for the subpopulations and not for the total population. [redacted]

[redacted]

13 DATA HANDLING AND RECORDKEEPING

By signing and dating the eCRF, the investigator will confirm that all studies have been completed and conducted in compliance with the CP, and that reliable and complete data have been entered into the eCRF.

13.1 Corrections to data

All data required by this CP 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 CP are to be entered into a sponsor-validated database of eCRFs.

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

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

13.2 Recordkeeping

Essential documents should be retained for a period of at least 10 years. Destruction of the documents after this period is only allowed after written agreement with the sponsor.

Essential documents at the study site include (among other documents):

- Source documentation (e.g., subject files, photos, scales).
- Subject identification code list (i.e., provided by template to the investigator, along with the ISF, at the beginning of the study), which identifies the subject by number, name, and date of birth.
- A signed copy of the final CP and any amendment.
- Investigator's compact disc/digital versatile disc with eCRF data, data clarification forms, and any associated subject-related source data (or, where applicable, authorized copies of source data).

- Signed informed consent forms.
- Copies of site investigators' and co-worker's curricula vitae.
- Copies of all direct correspondence with the EC (submission and approval letters).
- Copies of study supply receipt forms and device inventory forms.
- Copies of all essential correspondence between the investigator and the monitor, and between the investigator and the sponsor.
- Copies of safety information reported during the study and submitted by the sponsor.

13.3 Destruction of study documents

Study documents may not be destroyed by study site personnel prior to the retention period specified above without the prior written consent of the sponsor. The study institution must inform the sponsor in due time if the principle investigator leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

14 PUBLICATION POLICY

The study results should be published in the public domain, and publishing details will be given in the clinical study agreement. Publications concerning study results must be approved in advance by the sponsor in writing.

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 sponsor ensures that the study is registered, and study results are disclosed in at least one public clinical study registry, in accordance with national/international regulations and other requirements. Study registration may include a list of the study sites, as applicable.

15 REFERENCES

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16 APPENDICES

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