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Prospective, multicenter, parallel-group, evaluator-blind, randomized study to investigate the effectiveness and safety of MRZF111 in the treatment of décolleté wrinkles

Investigation identifier:	M930521001
IDE number:	Not applicable
Date of original clinical investigation plan and all previous amendments:	CIP Version 3.0 29-AUG-2019
Indication:	Improvement of décolleté wrinkles and skin quality
Planned investigation period:	First subject first visit: Dec-2019 Last primary outcome visit: Oct-2020 Last subject last visit: Feb-2021
Investigational medical device:	MRZF111
Sponsor:	Merz Pharmaceuticals GmbH Eckenheimer Landstr. 100 60318 Frankfurt/Main Germany Telephone: +49 69 1503 0 Telefax: +49 69 1503 200
Responsible for the clinical investigation plan content at the sponsor:	Clinical Project Manager: [redacted] Medical Expert: [redacted] Biostatistician: [redacted] Product Safety Officer: [redacted]
Coordinating Investigator: **Clinical investigation sites:**	[redacted] [redacted] [redacted] Germany
Statement:	This clinical investigation plan is defined in accordance with EN ISO 14155:2011

CONFIDENTIAL AND PROPRIETARY

SIGNATURE PAGE

The investigation will be conducted in compliance with the clinical investigation plan (CIP), EN ISO 14155, Declaration of Helsinki, and applicable regulatory authority requirements (e.g. MEDDEV 2.7/3).

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

[redacted] Date Signature

Aesthetics

[redacted] Date Signature

The following individuals also significantly contributed to the development of the CIP:

Coordinating Investigator	Date	Signature

Statement of Compliance

Investigation Site(s)

I have thoroughly read and reviewed the CIP. Having understood the requirements and conditions of the CIP, I agree to perform the clinical investigation according to the CIP, the electronic case report form (eCRF), EN ISO 14155, the Declaration of Helsinki, and regulatory authority requirements.

I have received the current investigators brochure (IB) and have been adequately informed about the investigational medical device (IMD) development to date, I also agree to:

Sign this CIP before the investigation formally starts.

Wait until I have received approval from the appropriate ethics committee (EC) before enrolling any subject in this investigation.

Obtain informed consent for all subjects prior to any investigation-related action performed.

Start the investigation only after all legal requirements in my country have been fulfilled.

Permit investigation-related monitoring, audits, EC review, and regulatory inspections.

Provide direct access to all investigation-related records, source documents, and subject files for the monitor, auditor, EC, or regulatory authority upon request.

Use the IMD and all investigational materials only as specified in the CIP.

Report to the responsible product safety officer, immediately, any adverse event that is serious, whether considered treatment-related or not, and any device deficiency that could have led to a SADE.

Furthermore, I understand that:

- Changes to the CIP 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 CIP is confidential and proprietary to Merz.
- Any deviation from the CIP may lead to early termination of the investigation site.

Principal investigator	Date	Signature
		Print Name
Investigation site stamp		

List of Abbreviations and Definitions of Terms

AE	Adverse event
ADE	Adverse device effect
ASADE	Anticipated serious adverse device effect
ASAPS	American Society for Aesthetic Plastic Surgery
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BfArM	Bundesinstitut für Arzneimittel; German Regulatory Authority
CaHA	Calcium Hydroxylapatite
CE	Communauté Européenne
CIP	Clinical investigation plan
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
[redacted]	
DRM	Data review meeting
EC	Ethics committee
eCRF	Electronic case report form
EU	European Union
FAS	Full analysis set
G	Gauge
GAIS	Global Aesthetic Improvement Scale
GAIS-Skin Quality	Global Aesthetic Improvement Scale on Skin Quality
GCP	Good clinical practice
HA	Hyaluronic acid
IB	Investigator's brochure
I.D.	Internal Diameter
IDE	Investigational Device Exemption
IU	International unit
iGAIS-Wrinkles	Investigator's Global Aesthetic Improvement Scale on Décolleté Wrinkles
iGAIS-Skin Quality	Investigator's Global Aesthetic Improvement Scale on Skin Quality
IMD	Investigational medical device
[redacted]	
ISO	International Organization for Standardization

LOCF	Last observation carried forward
MAS	Merz Aesthetic Scale
MedDRA	Medical Dictionary for Regulatory Activities
MPSV	German Ordinance on the Medical Device Safety Plan (Medizinproduktesicherheitsplanverordnung)
N	Number of non-missing observations
PPS	Per protocol set
PT	Preferred term
SAE	Serious adverse event
SADE	Serious adverse device effect
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SES	Safety evaluation set
sGAIS-Wrinkles	Subject's Global Aesthetic Improvement Scale on Décolleté Wrinkles
sGAIS - Skin Quality	Subject's Global Aesthetic Improvement Scale on Skin Quality
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
UTW	Ultra-Thin Wall
US	United States
USA	United States of America
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet

Definitions

Clinical Investigation Plan

CIP is synonymous with the term "protocol".

Effectiveness

Clinical effectiveness and performance shall be considered as synonymous for the purpose of this clinical investigation.

Investigation

The term "investigation" is synonymous with the term "study".

Evaluator

The term "evaluator" is synonymous with the term "rater".

RADIESSE®

The term "RADIESSE®" is synonymous with the term "RADIESSE® Volume Advantage 1.5 mL Injectable Implant".

MRZF111

"MRZF111" is the project specific term for the final applied IMD (RADIESSE® Volume Advantage 1.5 mL [redacted]). MRZF111 is prepared using a MRZF111 kit.

The term "MRZF111" is synonymous with terms "RADIESSE® Sub-brand" and "RADIESSE® Dilute".

MRZF111 kit

The term "MRZF111 kit" applies to the kit which is used to prepare a diluted implant (IMD MRZF111). [redacted]

Diluted RADIESSE®

The term "diluted RADIESSE®" refers to RADIESSE® Volume Advantage 1.5 mL Injectable Implant [redacted] with different mixing ratios when used in the Investigator Initiated Trials.

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1 SYNOPSIS

Investigation title

Prospective, multicenter, parallel-group, evaluator-blind, randomized study to investigate the effectiveness and safety of MRZF111 in the treatment of décolleté wrinkles.

Indication

Improvement of décolleté wrinkles and skin quality.

Investigation objectives

Primary objectives

- To evaluate the effectiveness and safety of MRZF111 treatment for improvement of décolleté wrinkles as assessed on the Merz Aesthetic Scale (MAS) Décolleté Wrinkles-At Rest.

Secondary objectives

- To evaluate the effectiveness of MRZF111 treatment for improvement of décolleté wrinkles as assessed on the MAS Décolleté Wrinkles-Dynamic.
- To evaluate the subjects and physician's treatment satisfaction assessment after MRZF111 treatment of the décolleté.
- To evaluate the subjects and physician's global aesthetic improvement on Décolleté Wrinkles (GAIS-Wrinkles) after MRZF111 treatment of the décolleté.

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

A total of approximately 112 adult females will be enrolled if they meet all of the inclusion and none of the exclusion criteria. The enrolment period will be 12 weeks in total.

Main inclusion criteria

- Female between ≥18 and ≤65 years old.
- Décolleté wrinkles with a rating of moderate to severe (grade 2 to 3) on the MAS Décolleté Wrinkles-At Rest as determined [redacted] and confirmed by the treating investigator afterwards.

Main exclusion criteria

- Any previous treatment with fat injections, poly L-lactic acid or permanent dermal fillers (e.g., silicone, polymethyl methacrylate) in the décolleté.
- Any previous surgery, including plastic surgery, or surgical permanent implant in the décolleté or in the breasts that could interfere with effectiveness and safety.

- Any previous thread lifting in the décolleté.
- Previous treatment with collagen fillers, calcium hydroxylapatite (CaHa), and/or long-lasting hyaluronic acid (HA) fillers (e.g., Belotero Intense/Volume, Juvéderm Volift/Volbella) in the décolleté within the past 24 months before baseline.
- Previous treatment with other HA fillers in the décolleté within the past 12 months before baseline.
- Previous treatment with botulinum toxin, ablative or fractional laser, microdermabrasion, microneedling, chemical peels and/or non-invasive skin-tightening (e.g., ultrasound, radiofrequency, intense pulsed light treatment) in the décolleté within the past 6 months before baseline.

Investigational medical device

The final applied IMD MRZF111 is RADIESSE® Volume Advantage 1.5 mL Injectable Implant [redacted]. The injection of MRZF111 needs to be done directly after dilution.

MRZF111 is prepared using a MRZF111 [redacted]

Investigation design

This investigation is 52-weeks prospective, multicenter, parallel-group, randomized clinical investigation with live assessments [redacted]

[redacted]. The treating investigators [redacted] that will participate in the investigation are board-certified dermatologists and/or plastic surgeons trained and qualified on the MAS. [redacted]

Approximately 112 female subjects with moderate or severe wrinkles (grade 2 or 3) on the MAS Décolleté Wrinkles-At Rest seeking improvement in décolleté wrinkles who agree to participate by signing the informed consent form and who satisfy all inclusion and exclusion criteria will be enrolled.

[redacted] aseline severity scores will be assessed live according to the MAS by the treating investigator [redacted] and the subject. Biophysical skin quality parameters (Cutometer®, Ultrascan®) and skin microstructure appearance [redacted] will be obtained instrumentally from each subject's treatment area by selected trained sites.

[redacted] either to treatment group A or treatment group B to the following treatment regimen:

- Treatment group A is assigned [redacted].
- Treatment group B is assigned [redacted].

A parallel-group design was chosen to evaluate two different treatment algorithms at once.

The primary objective of effectiveness for both treatment groups will be assessed at 16 weeks after last treatment (approximately Week 32). Response is defined as ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from baseline to 16 weeks after last treatment as assessed by [redacted] who is **not aware** of the treatment regimen.

[redacted] rating by the treating investigator, the subject self-assessment on the MAS (At Rest and Dynamic), and biophysical skin quality parameter measurements (at selected sites only) will be performed at baseline visit and at each follow up visit. [redacted]

Subject's and Investigator's Treatment Satisfaction Questionnaire, Global Aesthetic Improvement Scales on Décolleté Wrinkles (GAIS-Wrinkles) and Global Aesthetic Improvement Scale on Décolleté Skin Quality (GAIS-Skin Quality) will be completed at all follow-up visits.

[redacted] Medical safety assessment will be done at each follow up visit. **Planned investigational period**

First subject first visit: Dec-2019

Last primary outcome visit: Oct-2020

Last subject last visit: Feb-2021

Duration of treatment per subject

The duration of treatment is approximately 4 months per subject.

Endpoints for analysis

Primary Effectiveness Endpoint

Proportion of subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest scale at 16 weeks after last treatment compared to baseline (Day 1).

Secondary Effectiveness Endpoints

- Proportion of subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles – Dynamic scale at 16 weeks after last treatment compared to baseline (Day 1).
- Treating investigators treatment satisfaction assessment of aesthetic improvement in the subject after the décolleté treatments 16 weeks after last treatment.
- Subjects treatment satisfaction assessment of aesthetic improvement after the décolleté treatments 16 weeks after last treatment.
- Treating investigator's evaluation of the global aesthetic improvement on the investigator GAIS-Wrinkles (iGAIS-Wrinkles) from baseline (Day 1) [redacted] to 16 weeks after last treatment.
- Subject's evaluation of the global aesthetic improvement on the subject GAIS-Wrinkles (sGAIS-Wrinkles) from baseline (Day 1) [redacted] to 16 weeks after last treatment.

Secondary Safety Endpoints

- Incidence of TEAEs related to the treatment with the IMD.

Total number of subjects and number of countries

A total of approximately 112 adult females will be enrolled in Germany.

Number of investigation sites

Up to 10 sites.

Number of visits

Subjects are assigned to attend overall 6 visits [redacted] 24 or at latest 48 hours post-injection telephone contacts.

Investigational product(s), volume and mode of injection

The final applied IMD MRZF111 is RADIESSE® Volume Advantage 1.5 mL Injectable Implant [redacted]. The injection of MRZF111 needs to be done directly after dilution.

MRZF111 is prepared using a MRZF111 kit [redacted] Both groups (treatment group A and treatment group B) will be treated with [redacted] IMD at each injection visit [redacted]

Statistical analysis methods

The primary and secondary effectiveness endpoints will be summarized using the modified Full Analysis Set (FAS [redacted]. For sensitivity purposes, these analyses will also be performed on the modified FAS with observed data and on the Per Protocol Set (PPS). All remaining effectiveness endpoints will be summarized on the modified FAS population on observed data. Additional information related to the usage of the analysis sets as it relates to the statistical analyses of investigational results will be described in the Statistical Analysis Plan (SAP).

Statistical tests will be one-sided binomial tests at error level 2.5% for the response rates in general. [redacted] statistics will be provided for each endpoint for the pooled data and by realized treatment group. The supportive exploratory analyses for the primary effectiveness endpoint will also be performed on the observed cases in the FAS. Metric variables will be summarized by number of observations, mean, standard deviation, min. median and max. Categorical variables will be summarized by number and rate of events per category where the denominator will be chosen according to the adequate analysis population. Ordered categorical data will be summarized by metric and categorical statistics. All variables will be analyzed as absolute data and as change from baseline, as applicable.

If not otherwise specified confidence intervals in the following refer to two-sided 95% Wilson score confidence intervals.

All data captured in the electronic CRF will be listed.

Primary Effectiveness Endpoint

The primary effectiveness endpoint is the proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from baseline to 16 weeks after last treatment as assessed [redacted].

The primary analysis will be based on a one-sided binomial test at the one-sided type I error level of $\alpha = 0.025$ for the pooled data from both treatment groups to test the null-hypothesis that the response rate is $\leq 50\%$ versus the alternative that response rate is >50%:

As further supportive explorative analyses, the effectiveness for the different time points of treatments with a 16 weeks post-treatment period in both treatment groups will be analyzed on the observed cases in the modified FAS as for the primary endpoint:

- Proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from last treatment application to 16 weeks after last treatment as assessed [redacted] in treatment group A.

- Proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from last treatment application to 16 weeks after last treatment as assessed [redacted] treatment group B.

- Proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from baseline to 16 weeks after first treatment as assessed [redacted] in treatment group B.

In addition, two-sided 95% Wilson score confidence intervals will be provided overall, and for each treatment group in the supportive analyses.

Secondary Effectiveness Endpoints

One secondary effectiveness endpoint is the proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-Dynamic from baseline to 16 weeks after last treatment as assessed [redacted]. Same analyses as for the primary endpoint will be performed on this endpoint.

Number and percentage of subjects with any levels of treatment satisfaction of the aesthetic improvement in subject's décolleté at 16 weeks after last treatment assessed by investigator and subject will be calculated and the according 2-sided 95% confidence intervals for the percentage of subjects with any level of treatment satisfaction will be provided for the pooled treatments (overall).

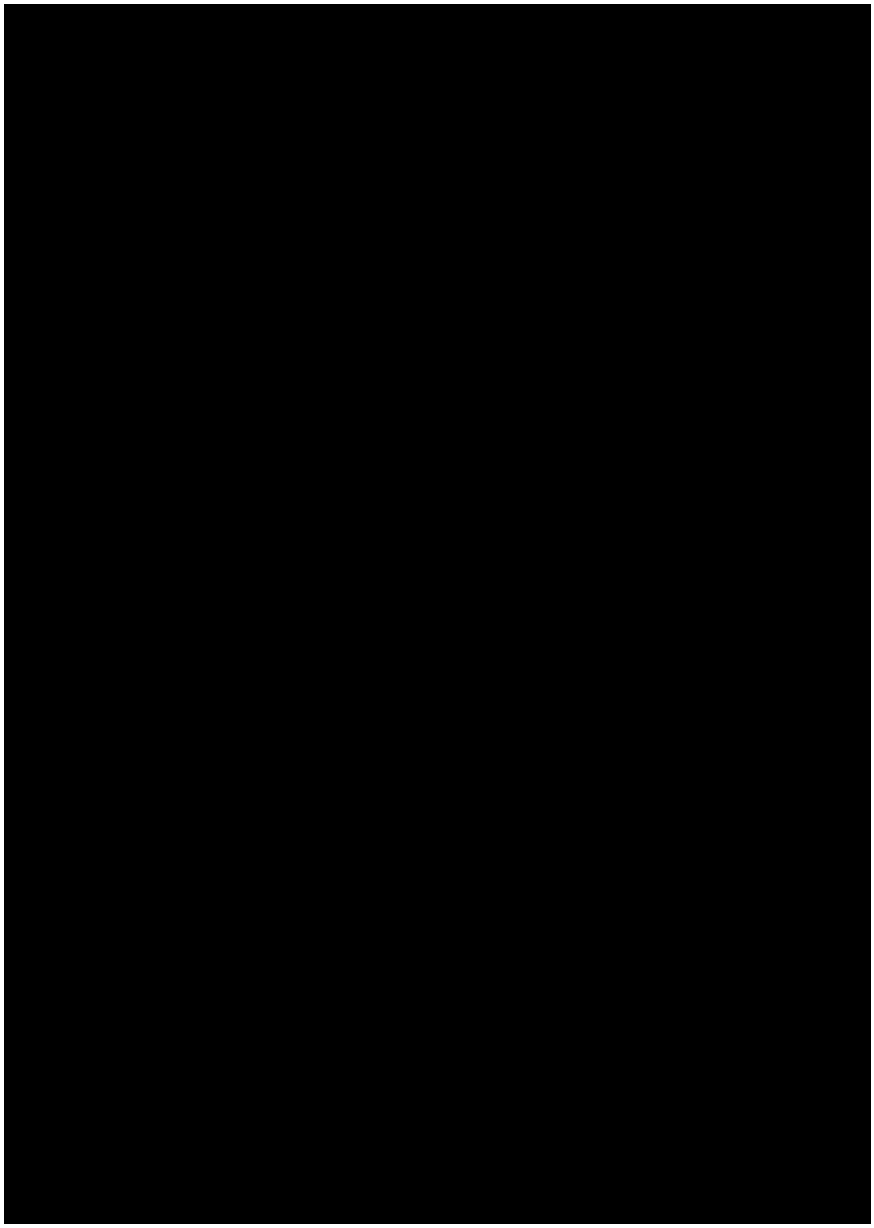
Number and percentage of subjects with improvement in iGAIS-Wrinkles defined in a rating of 1, 2 or 3 at 16 weeks after last treatment will be summarized and 2-sided 95% confidence intervals be provided overall. Analogous methods will be used for sGAIS-Wrinkles.

Secondary Safety Endpoints

All safety analyses will be performed on the Safety Evaluation Set (SES).

Only TEAEs will be analyzed, which are defined as AEs with onset on or after date of first injection of the IMD.

Incidences of TEAEs and SAEs will be provided by System Organ Class (SOC) and preferred term (PT). They will be provided overall and by worst intensity, by worst causal relationship and by worst outcome.



2 INVESTIGATION ADMINISTRATIVE STRUCTURE

2.1 Internal Responsibilities

Name	Function	Address
Merz Pharmaceuticals GmbH	Sponsor	Eckenheimer Landstrasse 100 60318 Frankfurt/Main Germany Telephone: +49-69-1503-0 Telefax: +49-69-1503-200
[redacted]	Clinical Project Manager	Telephone: [redacted] Telefax: Email:
	Medical Expert	Telephone: Telefax: Email:
	Regulatory Affairs Manager	Telephone: Telefax: Email:
	Biostatistician	Telephone: Telefax: Email:
	Product Safety Officer	Telephone: Telefax: Email:
	Data Manager	Telephone: Email:

2.2 External Responsibilities

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

Name	Function	Address
[redacted]		

3 ETHICS

3.1 Ethics Committee

The following documents must be submitted to and approved by the responsible EC:

- CIP,
- Amendments to CIP with a significant impact on the safety of the subjects or the scientific value of the investigation (if applicable),
- IB including its updates/amendments (if applicable),
- Subject information and informed consent forms, as well as updates (if applicable),
- All subject recruitment procedures and advertisements used to recruit subjects (if applicable),

[redacted]

- Any other required documents.

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

3.2 Ethical Conduct of the Investigation

This investigation will be conducted in accordance with the ethical principles of the Declaration of Helsinki, that are consistent with EN ISO 14155:2011 and the applicable regulatory requirements. Regulatory authorities will be notified and consulted as required prior to, during, and after the conduct of the investigation.

The clinical investigation shall not begin until the required approval/favorable opinion from the EC or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

3.3 Subject Information and Informed Consent

3.3.1 Subject Information

Prior to investigation 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 investigation. 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 and EN ISO 14155:2011 (chap. 4.7). The

obligations of the investigator are set forth in the CIP, EN ISO 14155:2011, 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 investigation prior to giving consent.

3.3.2 Informed Consent

Informed consent will be obtained in accordance with EN ISO 14155:2011 (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 briefings. The informed consent process must be traceable from the available documentation. At a minimum, this documentation should include information about when the subject was first informed about the investigation and who supplied the information. 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 investigation, the subject has to be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the investigation. In case of AEs, or poor tolerability to the IMD, the subject should inform the investigator, who then will make a judgment whether continuing in the investigation 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 Privacy

The subject will be informed of procedures to protect subject privacy. The Contract Research organization (CRO) and the sponsor processes subject data only in accordance with the data protection provisions set forth in the German Federal Data Protection Act (Bundesdatenschutzgesetz), specifically in the version applicable as of 25-MAY-2018, and in Regulation (EU) 2016/679 (General Data Protection Regulation). Informed consent on data processing will be obtained in writing directly from the subject before enrollment. Although recorded data will be passed on in a coded version only to authorized individuals, re-identification by the investigator (e.g., in case of emergencies) will be possible by the investigation 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 EC) who have been bound to confidentiality. If the results of the investigation are published, the subject's identity will remain confidential [redacted]

3.3.4 Contact Point

A contact address where subjects may obtain further general information regarding clinical investigations will be provided in the informed consent form.

3.4 Insurance

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

Any medical or non-medical deviation from the CIP that is deemed to have occurred through the subject's own fault may 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 CIP. The sponsor is also usually not liable for events resulting from negligence of the investigator, clinical investigational staff, and CRO, including failure to act according to EN ISO 14155:2011 or to comply strictly with the agreed CIP.

3.5 Financing

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

4 INTRODUCTION

4.1 Investigational Background

Skin aging

Skin, like many other organs, undergoes deleterious changes with the passage of time and is associated with hormonal and dietary variations. Unlike most other organs, however, skin is also directly affected by exposure to the environment, especially chronic Ultraviolet (UV) irradiation from the sun. UV exposure as part of extrinsic aging causes an aged phenotype (photoaging) that is superimposed with aging caused by chronological (intrinsic) aging. As a result, areas of the body that are frequently exposed to the sun such as the face, neck, forearms, or back of the hands acquire visible signs of aging more rapidly than other areas of the body [Rittie 2015, Shah 2018, Smith 2018]. Intrinsic skin aging is mainly related to oxidative stress due to an age-related decline in antioxidant capacity, and progressive telomere shortening associated with tissue damage. The rates of extrinsic and intrinsic aging vary considerably, based on individual exposure to the causative factors and hereditary predisposition. These processes result in skin laxity, folds, hypo- and hyperpigmentation, and surface changes, including skin roughness, atrophy, and xerosis [Sundaram 2016]. The décolleté in particular receives considerable sun exposure, and its skin is thinner than the skin of other areas, making it more vulnerable to extrinsic impact. In women, the décolleté is also subject to constant physical stress from the weight and movement of the breasts. Moreover, as a result of hormonal changes relating to menopause and estrogen deficiency, women are more prone to aging in this area. These changes result in an accelerated breakdown of collagen and elastin, leading to skin thinning and laxity, and worsening of lines and wrinkles [Casabona 2018]. Addressing these alterations is a major challenge for the aesthetic physician.

Surface treatment of the décolleté

Facial rejuvenation treatments with minimally invasive procedures have been established for some decades now [Sundaram 2016]. As a result, an interest in rejuvenation procedures for more challenging areas such as the neck and décolleté has increased in recent years. These exposed areas of the skin can reveal the actual age of a person although the face might look young after potential facial rejuvenation procedures.

The treatment of the décolleté is -in most cases- an off-label use. Physicians use a variety of topical cosmeceuticals, injectable implants (including RADIESSE®) and energy-based devices.

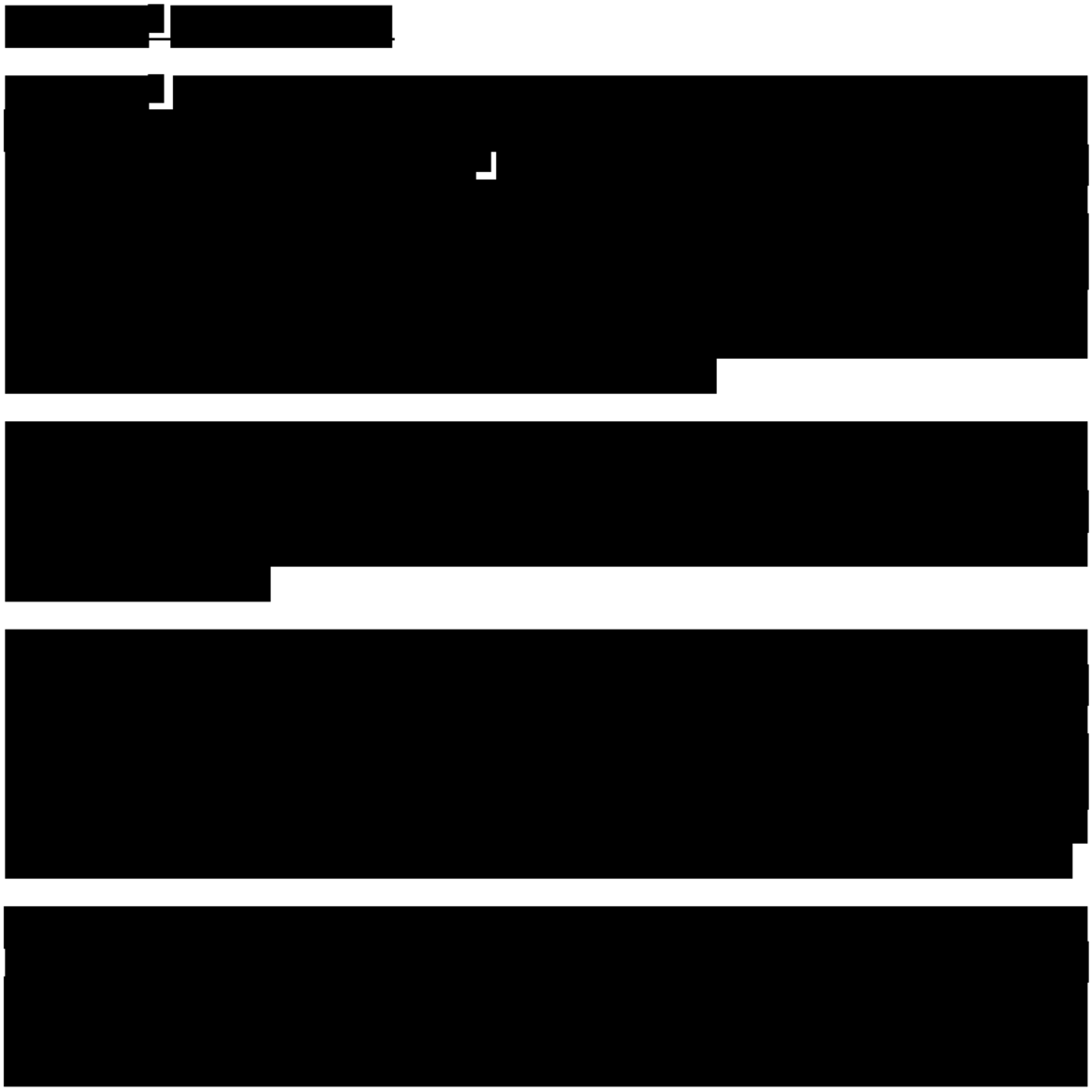
RADIESSE® in its original undiluted form is indicated for plastic/reconstructive procedures, including deep dermal and subdermal soft tissue augmentation of the facial area and is also intended for restoration and correction of facial volume loss. [redacted]

[redacted]. These alterations were histologically associated with increased collagen and elastin production [Yutskovskaya 2017, Zerbinati 2018]. Moreover, the treatment with diluted RADIESSE® has shown to be safe and was only associated with minor side-effects that are mostly transient and can easily be managed [Hevia 2009], thus representing an adequate injectable to address décolleté wrinkles. Dilution seems to allow a more homogeneous distribution of the material that may help to avoid complications such as granuloma formation [Devoto 2014].

Alternative therapies for the treatment of the décolleté with a comparable mode of action include other dermal fillers intended for the same indication. These fillers are primarily classified as permanent and non-permanent products. Permanent, i.e., non-biodegradable dermal fillers include polymethylmethacrylate microspheres with collagen, polymethylmethacrylate microspheres suspended in carboxygluconate gel, liquid silicone, saturated hydrocarbons, polymethylmethacrylate suspension, acrylic hydrogel particles suspended in HA, polyacrylamide gel, polyvinyl microspheres suspended in polyacrylamide, and e-polytetrafluoroethylene. Permanent fillers are hardly used any more today because they are prone to severe and persistent adverse effects [Wollina 2013]. Non-permanent, i.e., biodegradable, dermal fillers include HA, collagen (bovine, porcine, and human), poly-L-lactic acid, CaHA (like in RADIESSE®), subject's own body fat (autologous fatty tissue), and dextran beads in HA [Jordan 2015, Sachs 2011, Wollina 2013]. Non-permanent dermal fillers are safer than permanent fillers and usually associated with a low incidence of complications [Urdiales-Galvez 2018]. Various brands are available on the market, and the choice of the filler for a particular indication belongs to the practitioner and requires a solid knowledge of the products, injection techniques and human anatomy. The number of performed dermal filler procedures increases each year. According to an American Society of Aesthetic Plastic Surgeons (ASAPS) statistics report, 2.7 million soft tissue filling procedures have been performed in 2017 in the USA alone, representing a 3% increase from the previous year [ASAPS 2018].

Other alternative therapies have different modes of action and can thus be performed as complimentary procedures for the best global aesthetic improvement and high patient satisfaction. Botulinum toxin is injected in the muscles to address dynamic wrinkles. It produces temporary chemical denervation by blocking the presynaptic release of acetylcholine at the neuromuscular endplate [Ali 2007, Ganceviciene 2012]. Topical cosmeceuticals address skin quality improvement and potentially slow down skin wrinkling. Their active ingredients include substances such as retinoids, alpha hydroxyl acids, ascorbic acid, vitamin E, alpha-lipoid acid, niacin amide, N-acetyl-glucosamine, resveratrol, flavonoids, grape seed extract, isoflavones, tea phenols, dimethylaminoethanol and moisturizes [Bowler 2009]. Some drugs have been shown to exert a certain anti-aging effect when applied topically, including hormones, vitamin A derivatives, 5-flourouracil, and imiquimod [Konda 2013], as well as photodynamic therapy [Szeimies 2013]. Ablative resurfacing techniques address skin quality improvement by wounding the skin at different layers, and thus initiating a healing process, which can result in a smoother and firmer skin. The available tools include peeling agents, dermabrasion and various energy devices [Ali 2007]. Chemical peels exfoliate the upper skin surface layer in a controlled manner.

Medium and deep peels can also induce neocollagenesis, and thus improve fine lines and wrinkles. The agents are typically composed of trichloroacetic acid >30%, strong Jessner's solution, resorcinol, and low concentration phenol [Ali 2007, Ganceviciene 2012, Konda 2013]. Dermabrasion mechanically removes the epidermis and dermis, usually with a diamond powered fraise [Ali 2007]. Laser resurfacing devices (e.g. carbon dioxide and erbium) vaporize skin cells damaged at the surface level. Fractionated lasers emit coherent light in a pixelated manner onto the skin producing an array of microthermal zones in the dermis. The resulting controlled thermal stress is followed by a wound healing response leading to reepithelization and dermal remodeling [Ganceviciene 2012]. Radiofrequency devices generate heat to produce subtle damage to collagen and a subsequent inflammatory response leading to skin tightening effect [Konda 2013]. Ultrasound devices apply precise pin-point heating to induce collagen contraction and denaturation, and thus initiate its aggressive synthesis. Wound-healing response stimulates long-term tissue remodeling and leads to further lifting and tightening [Baumann 2016, Gutowski 2016].



[redacted]

4.2 Investigational Rationale

Essential features of safe and effective dermal fillers include minimization of adverse effects, facility of use, and longevity of results. The purpose of this investigation is to collect clinical data on MRZF111 when used in the décolleté [redacted] to confirm its clinical performance and safety, acceptability of identified residual risks, and to detect emerging risks based on factual evidence.

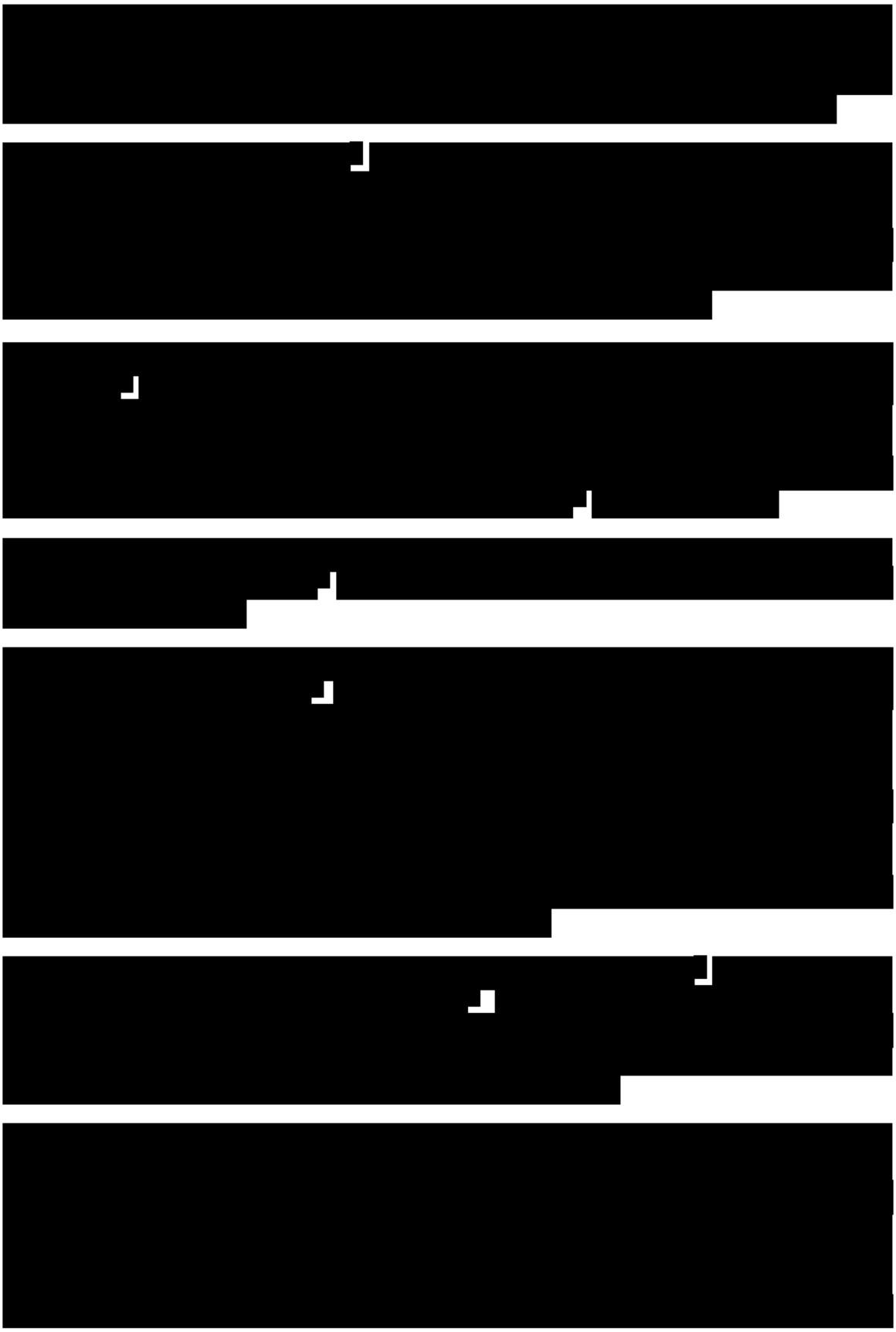
[redacted] Highly viscoelastic, CaHA is well suited for supraperiostal, subdermal, and deep-dermal placement and can deliver considerable volumizing effect. However, it is common practice among physicians to use RADIESSE® in a diluted form to address skin areas with a broader surface such as hands, neck and décolleté. Dilution makes the product less viscous and therefore more suitable for rejuvenation treatments of such areas without the volumization effect. Diluted CaHA has been shown to be effective and safe for the treatment of atrophic hands [Emer 2013, Goldman 2018]. Amselem and Cogorno Wasylkowski published the first reports demonstrating noticeable improvements in skin firmness and appearance after injection of CaHA diluted with small amounts of lidocaine in the arm, abdomen, and thighs [Amselem 2016, Cogorno Wasylkowski 2015].

[redacted]

[redacted] Improvement in skin elasticity and pliability and increased dermal thickness translate to visible aesthetic improvements and subject satisfaction. [redacted] With the investigation proposed in this CIP, we want to collect further data on the performance and the safety of diluted CaHA in the décolleté and to determine the appropriate treatment regimen.

[redacted]

An evaluation of biological safety was performed. Most biocompatibility studies were performed with the RADIESSE® Injectable Implant (which is already CE-marked). [redacted]



[redacted]

Overall, clinical evidence suggests that dilution of RADIESSE® is as safe as the original CE-marketed undiluted preparation for which the excellent safety profile has long been established. The components of the mixing kit are already CE marked. The main focus of the proposed investigation lays therefore on the collection of performance data of the IMD in the décolleté to further support its beneficial properties in this indication.

4.3 Risk Analysis and Benefit-Risk Assessment

4.3.1 Anticipated Clinical Benefits

- According to clinical studies, the treatment will lead to an improvement of décolleté wrinkles.

[redacted]

- 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 2018, 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 2018, Sadick 2007].

[redacted]

- 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 usually 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 RADIESSE® in its original un-diluted form is marketed for aesthetic since 2003 in the European Union (EU) and is also registered and marketed in over 50 countries worldwide. Since then, over 5 million units had been sold. As it has already been used in a variety of subject populations.

4.3.2 Anticipated Adverse Device Effects

Study subjects must be informed that as with any implant material possible adverse reactions may occur:

- Swelling, edema, festoons, angioedema
- Induration, mass, nodules, lumpiness and granulomas at the injection site, calcium deposits

- Erythema, redness
- Pain, tenderness, soreness
- Loss of effect, reduced effect (undercorrection, under injection), overcorrection (over injection), superficial injection, delayed reaction
- Discoloration, hyperpigmentation, depigmentation, blanching
- Bruising, ecchymosis
- Embolia cutis medicamentosa, skin necrosis, vascular occlusion (obstruction), ischemia
- Numbness, hypoaesthesia, hyperaesthesia, parasthesia (tingling), burning sensation
- Inflammation, foreign body inflammation
- Product migration/displacement, tissue plane migration
- Itching, pruritus
- Haematoma, bleeding, petechiae,
- Allergy, allergic reaction, hypersensitivity, anaphylaxia
- Infection (e.g., impetigo), abscess, pus, cellulitis
- Rash, urticaria (hives), contact dermatitis
- Dizziness, blurred vision, headache, nausea, hyperventilating, syncope, malaise (flu-like symptoms, shakes/chills), tachypnea, pericarditis
- Warmth
- Exfoliation, scab, abrasion
- Pustules, papules, pimples
- Contour irregularity, asymmetry, unevenness, uneven contours
- Paralysis
- Blisters, vesicles
- Herpes reactivation (herpes simplex, herpes zoster)
- Fever
- Lymphadenopathy, lymphoedema
- Irritation
- Scarring
- Dryness, hair loss, ptosis
- Tightness
- Muscle twitching
- Guillain-Barre syndrome
- Veins look more prominent, broken capillaries
- Sarcoidosis
- Sensitivity to cold
- Extrusion
- Granulomatosis with Polyangiitis

- Stroke
- Introduction of the IMD into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying skin structures. This complication is more likely when the IMD is injected into the lips, nose, glabellar or ocular area. In a large cross-sectional review, this risk was considered low (<0.01%) [DeLorenzi 2014, Rayess 2018].
- The following adverse events were reported during clinical studies performed with RADIESSE® Injectable Implant: ecchymosis, edema, erythema, granuloma, nodule, pain, pruritus, soreness, tenderness, numbness, contour irregularity, lumps, rash, discoloration, hardness, headache, scab, tightness, abrasion, burning sensation, papule/pustule, firmness, hearing loss, swelling and, nausea. For cases where information was available, patients had recovered or were recovering with minimal to no scarring at last contact. Few cases required consultation with a plastic surgeon and possible excision and revision surgery to correct the defect resulting from the necrosis (see current IB and Risk Analysis [IB, Risk Analysis]).
- A detailed list of adverse events obtained from Post Marked Surveillance for RADIESSE® Injectable Implant can be found in the current IB [IB]. The nature, intensity, and duration were comparable to those reported during studies.

- Since the IMD is biodegradable, regular follow-up treatment may be necessary if a visible enhancement effect (optimal cosmetic correction) continues to be desired.
- As with any other medical treatment, injection with the IMD may be associated with unforeseen and/or unanticipated AEs. For further information see current version of the IB [IB].

Investigators must be informed that as with any medical device the following Adverse Device Effects (ADEs) may occur:

- Needle breakage
- Leakage of material
- Resistance during injection, needle jamming
- Injury of third persons (e.g., during detachment of needle after treatment procedure).

4.3.3 Residual Risks Associated with the Investigational Device, as Identified in the Risk Analysis

All risks detected during risk management were mitigated to levels deemed acceptable. For a detailed list of all risks please refer to the current Risk Analysis Report [Risk Analysis].

4.3.4 Risks Associated with Participation in the Clinical Investigation

Any subject that is enrolled in this clinical investigation and has received injection with the IMD can potentially encounter one or more side effects that are described in Section 4.3.2. or with unforeseen complications. This can potentially lead to transient or permanent impairment, and/or incapacity to work, and/or restrictions in daily routine.

4.3.5 Possible Interactions with Concomitant Medical Treatments

- The IMD can interact with other implantable materials.

[redacted]

4.3.6 Steps that will be Taken to Control or Mitigate the Risks

To control the above-mentioned risks, the following steps will be taken to control them as best possible:

- The investigator is not allowed to inject the IMD into other areas than the décolleté [redacted]
- The investigator is not allowed to inject the IMD into the skin prone to developing inflammatory skin conditions, or with a tendency for developing hypertrophic scars or keloids; in subjects with systemic disorders which cause poor wound healing or will lead to tissue deterioration over the implant.

- As the IMD can interact with other implantable materials, it is only allowed to inject the IMD when potential injectable material in the décolleté has completely resorbed at baseline; it is not allowed to inject the IMD in the area previously treated with permanent dermal fillers.

- The investigator is obliged to discuss all potential risks of IMD injection with the subjects prior to treatment and to ensure that the subjects are aware of signs and symptoms of potential complications.

- As the subject may experience slight discomfort during and following the procedure, anesthetic techniques like topical anesthetics or cooling are allowed in this investigation.
- The components of the MRZF111 kit should be carefully examined to verify that neither the packaging nor the devices have been damaged during shipment. The MRZF111 kit must not be used if the packaging of any of the components is compromised or if any of the devices have been damaged or if the syringe end cap or syringe plunger is not in place.

- The usual aseptic practices and precautions associated with percutaneous injection procedures should be followed to prevent infection.

[redacted]

- To avoid needle breakage, the investigator will be advised to not attempt to straighten a bent needle but to replace it.

[redacted]

- Infection requiring treatment may occur at the injection site. It generally results from natural skin flora being introduced through the injection site. These infections often respond to oral antibiotics [Rayess 2018]. If such infection cannot be corrected, it may become necessary to perform an invasive medical procedure.

[redacted]

- Irregularities of the skin may occur after the treatment which may require a surgical procedure to correct.

[redacted]

- As the injection with the IMD may be associated with unforeseen and/or unanticipated AEs, regular safety follow-up visits will be scheduled, and the subjects will be instructed to contact the site without delay in any case he/she suspects an ADE.
- Used and partially used syringes and injection needles should not be recapped and be handled and disposed in an appropriate sharps or biohazard container.

4.3.7 Benefit-to-Risk Rationale

The RADIESSE® in its original un-diluted form is marketed for aesthetic treatments and is indicated for plastic and reconstructive surgery, including deep dermal and sub-dermal soft tissue augmentation of the facial area, and is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus since 2003 in the EU, and is also registered and marketed in over 50 countries worldwide. Since then, over 5 million units had been sold. As 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. By diluting the original product, side effects will probably not occur more often. Some side effects, such as nodules and granuloma, might occur less often.

Clinical data collected from available publications on RADIESSE® Injectable Implant diluted with normal saline solution at various dilution ratios demonstrate:

- the safety and effectiveness of [redacted] RADIESSE® [redacted]
- high patient satisfaction for all applications of diluted RADIESSE®

The mixing kit and in-depth description of the mixing procedure for MRZF111 assure that investigators or delegated staffs are guided in the preparation and handling of MRZF111 before injection. This aspect contributes to and optimizes the benefit-to risk-ratio for the subject, assuring the intended dilution and maintaining sterility.

Considering all risks and benefits of the IMD the potential benefits to physicians and subjects seeking treatment outweigh the potential risks (Section 4.3.6). The benefit/risk ratio of the device is considered as acceptable when used on subjects with décolleté wrinkles.

5 INVESTIGATION OBJECTIVES

Primary objectives

- To evaluate the effectiveness and safety of MRZF111 treatment for improvement of décolleté wrinkles as assessed on the MAS Décolleté Wrinkles-At Rest.

Secondary objectives

- To evaluate the effectiveness of MRZF111 treatment for improvement of décolleté wrinkles as assessed on the MAS Décolleté Wrinkles-Dynamic.
- To evaluate the subjects and physician's treatment satisfaction assessment after MRZF111 treatment of the décolleté.
- To evaluate the subjects and physician's global aesthetic improvement (GAIS-Wrinkles) after MRZF111 treatment of the décolleté.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 General

This investigation is a 52-weeks prospective, multicenter, parallel-group, randomized clinical investigation [redacted] A parallel-group design was chosen to compare two different treatment regimens. Up to 10 sites were chosen to improve data homogenization and to minimize site-associated biases. The treating investigators [redacted] that will participate in the investigation are board-certified dermatologists and/or plastic surgeons trained and qualified on the MAS. The [redacted] that will participate in the investigation are physicians or scientific experts, experienced in the area of aesthetic medicine, and also trained and qualified on the MAS.

Approximately 112 subjects with moderate or severe wrinkles (grade 2 or 3) on the MAS Décolleté Wrinkles-At Rest seeking improvement in décolleté wrinkles who agree to participate by signing the informed consent form and who satisfy all inclusion and exclusion criteria will be enrolled in Germany.

[redacted] Baseline severity scores [redacted] according to the MAS by the treating investigator [redacted] and the subject. [redacted]

[redacted]

[redacted]

Number of visits:

Subjects are assigned to attend overall 6 visits [redacted] 24 or at latest 48 hours post-injection telephone contacts. On injection visits, all investigation assessments will be conducted **before injection**.

The primary objective of effectiveness for both treatment groups will be assessed at 16 weeks after last treatment (approximately Week 32). Response is defined as ≥1-point improvement on the MAS Décolleté Wrinkles-At Rest from baseline to 16 weeks after last treatment as assessed [redacted] who is **not aware** of the treatment regimen.

[redacted] the [redacted] rating by the treating investigator, the subject self-assessment on the MAS (At Rest and Dynamic) [redacted] will be performed at baseline visit and at each follow up visit [redacted]

Subject's and Investigator's Treatment Satisfaction Questionnaire, GAIS-Wrinkles, and GAIS-Skin Quality will be completed at all injection and follow-up visits.

[redacted]

For details on the primary and secondary endpoints please refer to Section 12.3. For the rationale of the selection of primary and secondary endpoints and their measurements please refer to Section 6.2.

If any SAE related to the injection or the IMD is not resolved by the end of the investigation, the subject will be followed-up until the resolution of the SAE by Merz Pharmaceuticals Global Product Safety Department.

Subjects that prematurely discontinue the study will not be replaced.

[redacted]

[redacted]

6.1.2 *End of Investigation*

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

6.2 Discussion of Investigational Design, Including Choice of Control Groups

The prospective, parallel-group, randomized, [redacted] multicenter investigational design was chosen to adequately investigate the effectiveness and safety of the IMD.

In general, prospective designs can achieve a higher data quality compared to retrospective designs because they usually have fewer potential sources of bias and confounding than retrospective studies. A disadvantage of prospective studies is the risk of bias such as the loss of individuals to follow up during the investigation.

Up to 10 sites were chosen to improve data homogenization and to minimize site-associated biases. Using several investigation sites increases the representativeness of the investigational results and decreases investigation site-related biases.

[redacted]

All the [redacted] do not know which treatment protocol was applied (either 2 or 3 injection cycles) which helps minimize bias due to demand characteristics (what the evaluator expects). As this investigation has no control group, the subject and the treating investigator cannot be blinded. [redacted]

A parallel-group design was chosen to evaluate two different treatment algorithms at once. Randomization eliminates bias in treatment assignment, specifically selection bias and confounding.

[redacted]The general duration of 52 weeks will also allow assessing the late-onset reactions [Bass 2010, Smith 2007].

[redacted]

The injection technique approach follows the consensus guidelines mentioned above: the IMD has to be placed in th [redacted].

7 INVESTIGATION POPULATION

7.1 Selection of Investigation Population

A total of approximately 112 adult females will be enrolled in Germany if they meet all of the inclusion and none of the exclusion criteria. Point of enrollment is the time at which, following recruitment, the subject signs and dates the informed consent form.

Investigators may recruit subjects from their existing pool of subjects, new subjects that are seeking 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.

7.2 Inclusion Criteria

Only subjects meeting all of the following inclusion criteria will be considered for investigational enrollment:

Inclusion Criteria	Rationale
[redacted]	
Female between ≥18 and ≤65 years old.	Administrative
[redacted]	
Décolleté wrinkles with a rating of moderate to severe (grade 2 to 3) on the MAS Décolleté Wrinkles-At Rest as determined [redacted] and confirmed by the treating investigator afterwards.	Effectiveness
[redacted]	

[redacted]

7.3 Exclusion Criteria

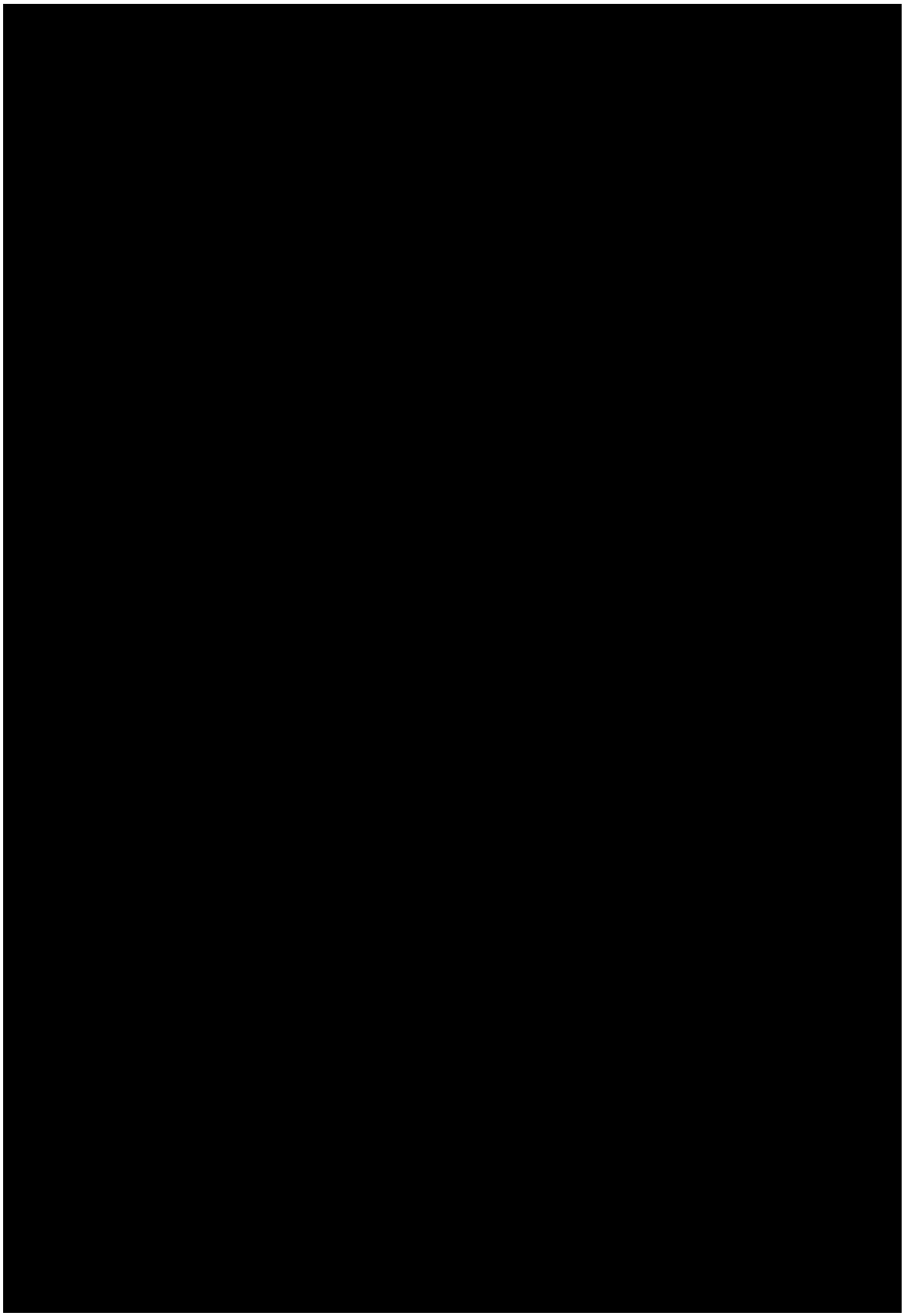
Subjects having any of the following criteria, either at screening or at baseline, will not be included in the investigation:

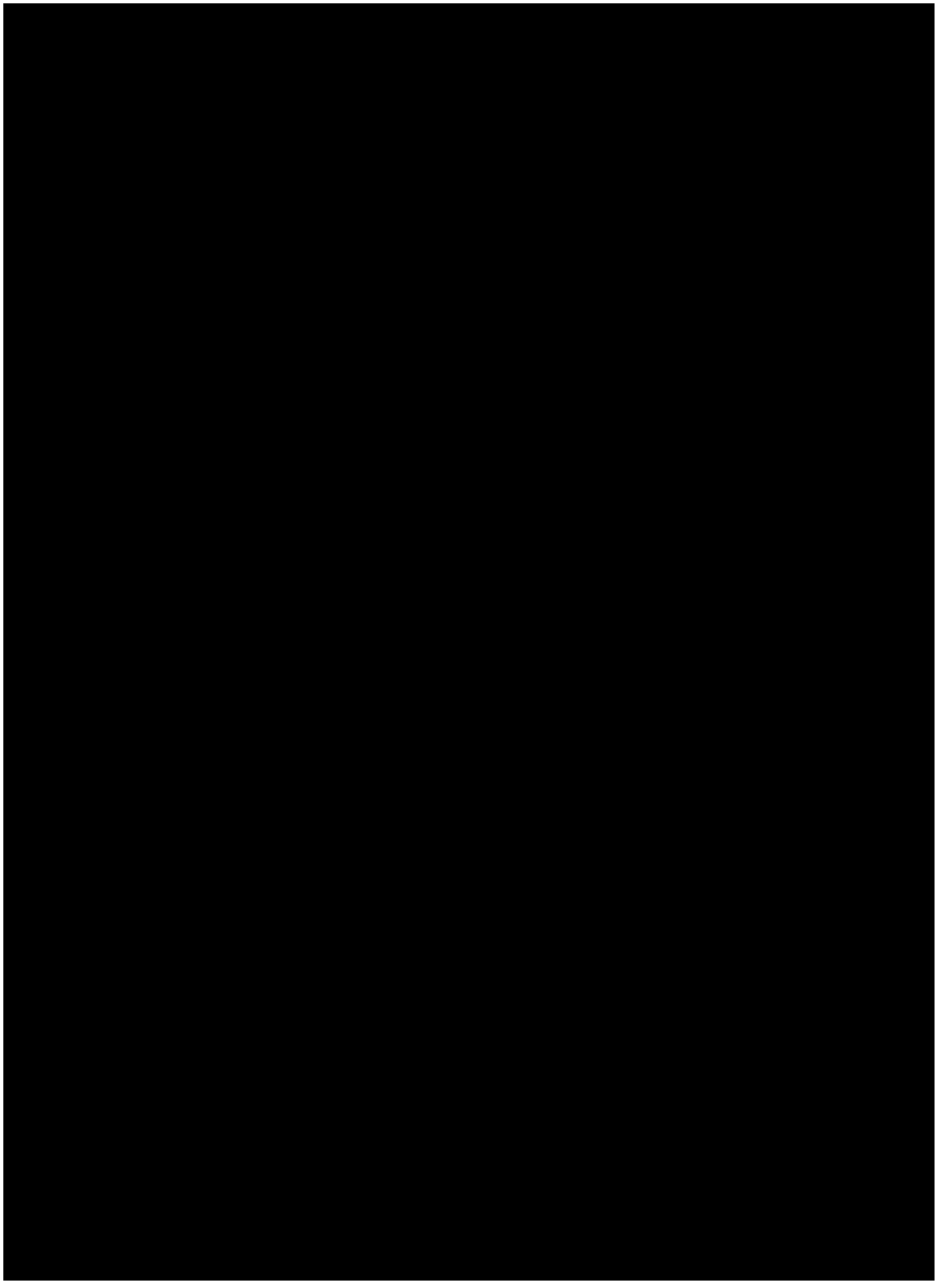
Exclusion Criteria	Rationale
Any previous treatment with fat injections, poly L-lactic acid or permanent dermal fillers (e.g., silicone, polymethyl methacrylate) in the décolleté.	Safety concern
Any previous surgery, including plastic surgery, or surgical permanent implant in the décolleté or in the breasts that could interfere with effectiveness and safety.	Safety concern Effectiveness
Any previous thread lifting in the décolleté.	Safety concern
Previous treatment with collagen fillers, CaHA, and/or with long lasting HA fillers (e.g., Belotero® Intense/Volume, Juvéderm® Volift/Volbella) in the décolleté within the past 24 months before baseline.	Safety concern

[redacted]

Exclusion Criteria	Rationale
[redacted] Previous treatment with other HA fillers in the décolleté within the past 12 months before baseline.	Safety concern
Previous treatment with botulinum toxin, ablative or fractional laser, microdermabrasion, microneedling, chemical peels and/or non-invasive skin-tightening (e.g. ultrasound, radiofrequency, intense pulsed light treatment) in the décolleté within the past 6 months before baseline.	Safety concern

[redacted]





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 investigation at any time without any penalty or loss of benefits to which the subject is otherwise entitled (see Section 7.4.3). Premature discontinuation of the investigation with its reason(s) must be recorded in the subject file and the eCRF. Date and discontinuation circumstances should be stated.

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

- Withdrawal of informed consent.

- Pregnancy (no further injection of IMD, or any other interventional procedure will be performed).
- Any AEs for which treatment continuation would constitute an unacceptably high risk for the subject.

CIP deviations or conditions arising from the exclusion criteria established in Section 7.3, may lead to the subject's discontinuation. All such conditions should be properly documented.

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

Following discontinuation, a final examination 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 telephone contact, copies of letters).

7.4.2 Premature Termination or Suspension of the Investigation or an Investigation Site

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

- Subject enrollment is unsatisfactory.
- The benefits and risks of continuing the investigation have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data on the IMD do not justify a continuation of the investigation.
- The investigator or investigation site exhibit serious and/or persistent non-adherence to the CIP, Declaration of Helsinki, EN ISO14155:2011, and/or applicable regulatory requirements.
- The sponsor decides to terminate the investigation at any time for any other reason.

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

If the investigation 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, investigation sites, the EC, and regulatory authorities of the termination or suspension of the investigation, as well as provide reasons for the action.

7.4.3 Provision of Care for Subjects after Investigation Discontinuation

Plans for treatment or care after investigational discontinuation are not foreseen, as this is an investigation without therapeutic relevance.

8 TREATMENTS

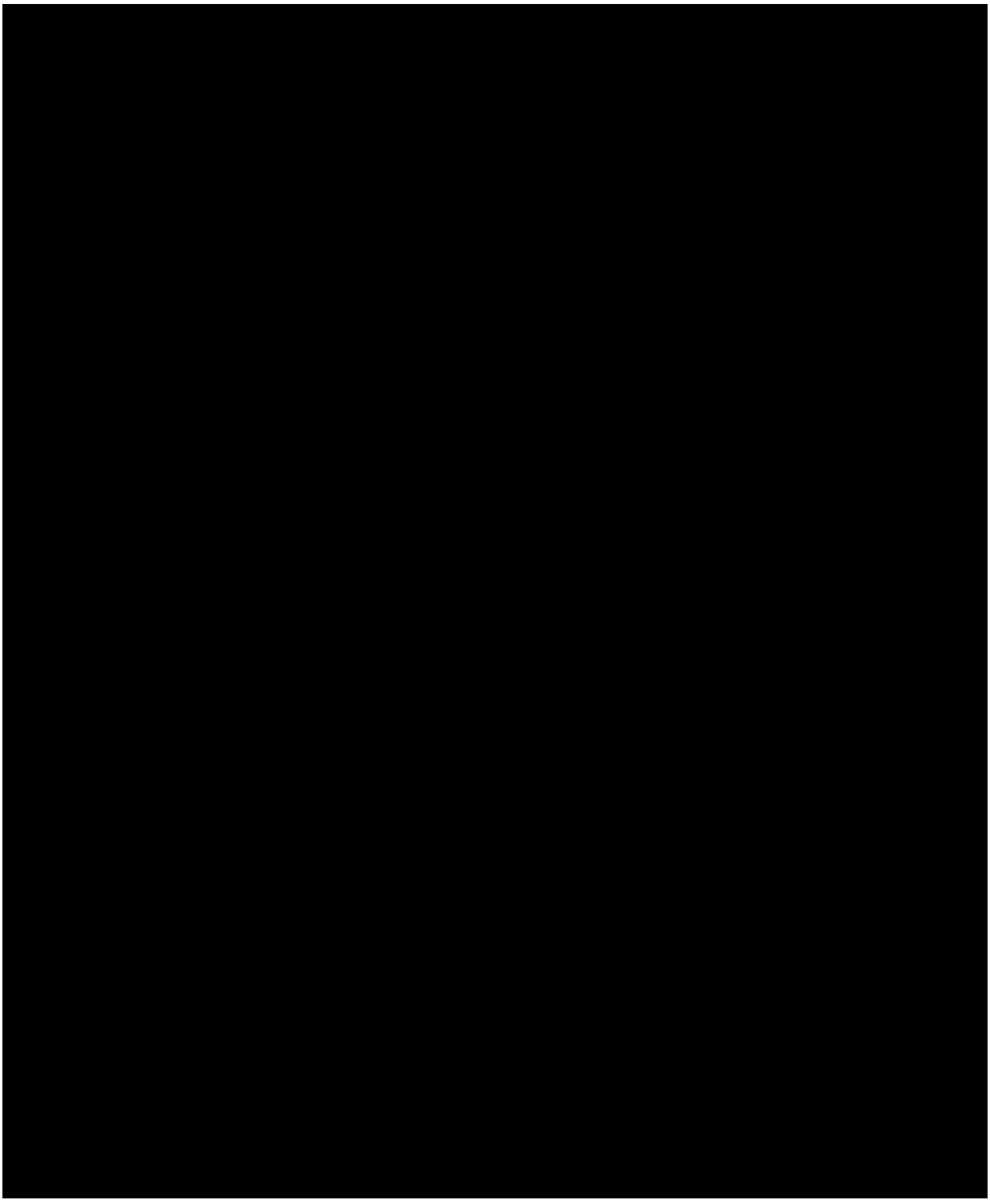
8.1 Investigational Medical Device(s)

8.1.1 Description of Investigational Medical Device(s) and its Intended Purpose in the Present Clinical Investigation

8.1.1.1 Investigational Medical Device(s)

The final applied IMD MRZF111 is RADIESSE® Volume Advantage 1.5 mL Injectable Implant [redacted]. The injection of MRZF111 needs to be done directly after dilution.

[redacted]



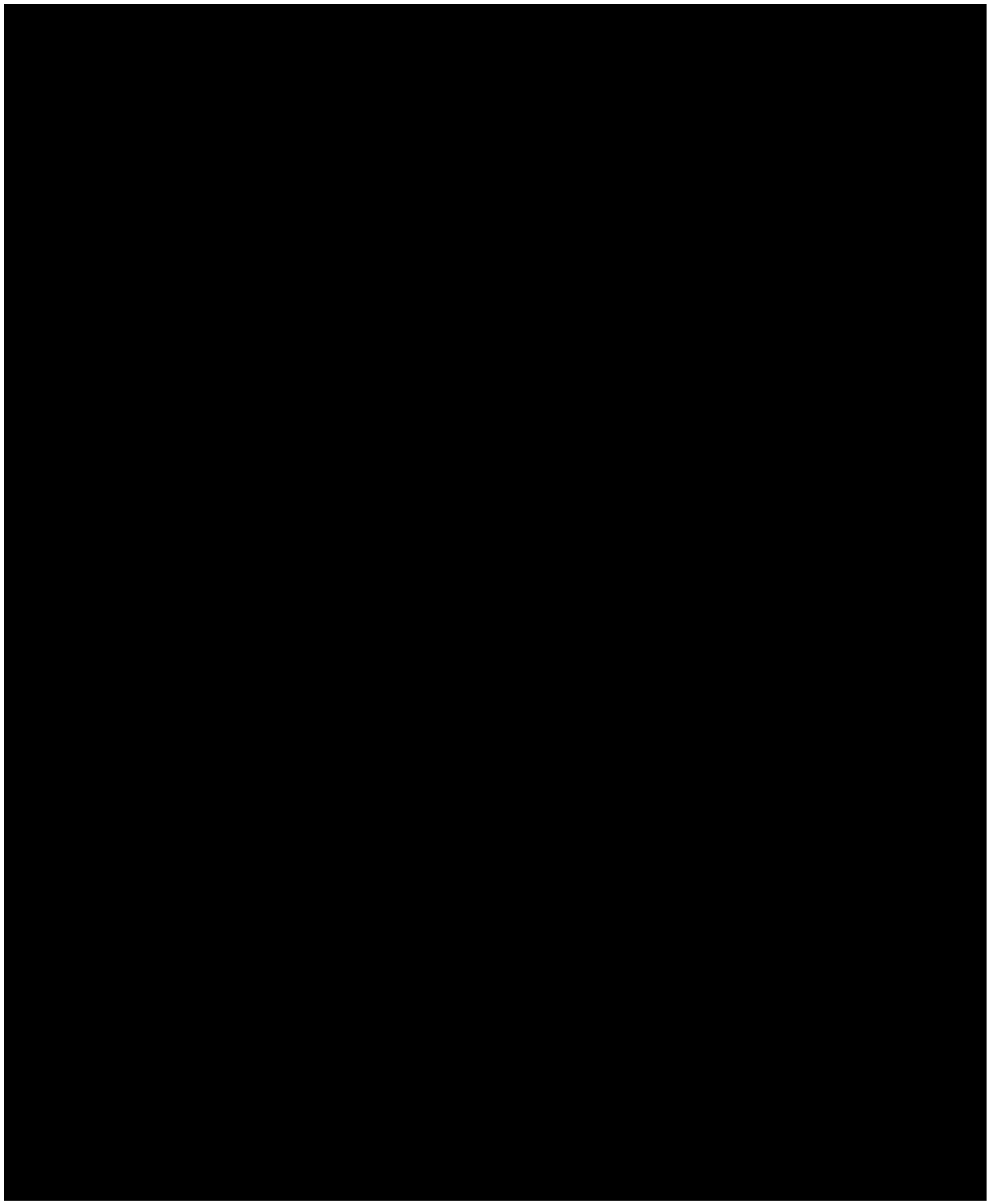
The intended purpose of the IMD in the present clinical investigation is the [redacted] injection of the IMD in the décolleté. For further details on the injection technique, please refer to Section 8.1.3. Only physicians who are highly experienced in the treatment of the décolleté with injectable fillers (preferably with CaHA) are allowed to conduct this investigation.

8.1.2 Instructions for Preparation

Both groups (treatment group A and treatment group B) will be treated in the décolleté area with MRZF111. [redacted]

MRZF111 must be used immediately after preparation.

[redacted]



8.1.3 Instructions for Application

Prior to treatment, the subject's medical history should be obtained, and the subject should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration.

The subject must be prepared for percutaneous injection using standard methods. The treatment injection site should be prepared with a suitable antiseptic. Apply local or topical anesthesia at the injection site or ice to the area to decrease local swelling/distention or sedation could be used at the discretion of the investigator.

[redacted]

The investigator should locate the initial site for the implant. It is not allowed to inject into scar tissue or into a blood vessel. [redacted] ver-correction is not allowed.

[redacted]

It is recommended to mold or massage the injected implant periodically during the injection process to maintain a smooth distribution and integration of the implant.

Following treatment, manual massage of the entire treatment area can be performed by the treating investigator in order to promote even distribution of MRZF111.

The investigator will use the IMD and all investigational materials only within the framework of the clinical investigation and in accordance with this CIP.

8.1.4 Packaging and Labeling

The packaging and labeling will be according to regulatory requirements and specifications in Germany. The labelling that of the outer box is with additional labelling of "Studiennummer: M930521001", and „Medizinproduktenummer: XXXX"(MRZF111 kit number with sequential numbering).

MRZF111 kits will be provided directly to the investigation sites at the beginning of the investigation. Replenishments will be provided during the investigation, if necessary.

8.1.5 Storage of Investigational Medical Device

Storage temperature (a controlled room temperature between 15°C and 32°C) will be controlled once a week and the minimum/maximum temperature will be recorded in a temperature log.

8.1.6 Accountability for Investigational Medical Device

It is the responsibility of the investigator according to German law to ensure that a current record of inventory accountability per site and per investigational subject is maintained. Inventory records must be readily available for inspection by the unblinded investigational monitor and are open to inspection by regulatory authorities at any time. Each shipment of materials for the investigation will contain an MRZF111 kit supply and return form to assist the investigator in maintaining current and accurate inventory records. This form includes the following information: investigation number, dates, quantities, LOT number, expiration date, and the sequential numbering code number assigned to the MRZF111 kit.

Upon receipt of the MRZF111 kits, the investigator according to German law will visually inspect the shipment and verify the number and condition of the IMD. The MRZF111 kit supply and return form will be completed and signed by the investigator or authorized investigation site staff according to local law. The completed form should be sent to the sponsor or the designated warehouse, 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 at regular intervals by the monitor. The results of the inspection will be made available to the authorized individuals (e.g., unblinded monitor, auditor, and regulatory authorities) on request throughout the investigation.

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

8.1.7 Destruction of Investigational Medical Device

Upon the completion or termination of the investigation, all unused MRZF111 kits must be returned to the sponsor or delegated warehouse. The sponsor or warehouse will destroy the MRZF111 kits after completion of the clinical investigation report. Destruction of unused MRZF111 kits at the study site may be possible if written authorization is provided by the sponsor. If destruction at the study site is agreed upon, then a certificate of destruction must be given to the sponsor.

For safety and to prevent cross-contamination, all used disposable needles and cannulas must be discarded in an appropriate sharps or biohazard container. The used IMD has to be destroyed on site too.

8.2 Treatments Administered

MRZF111 will be applied according the administration method described in Section 8.1.3.

[redacted]

8.2.1 Methods of Assigning Subjects to Treatment Groups

The investigation is planned as a multicenter investigation. Subjects will be assigned to treatment groups according to a balanced randomization. Balanced randomization in blocks of appropriate size and blockwise distribution of the IMD to the treatment groups (treatment group A, treatment group B) ensure an approximately equal number of enrolled subjects in every treatment group. The block size will not be disclosed to the evaluators.

The responsible randomization officer will conduct the random allocation of treatments to subjects using a validated computerized randomization program. Subjects will receive the lowest available randomization number, which will be recorded along with the date of randomization in the eCRF.

[redacted]

8.2.3 Selection and Timing of Exposure for Each Subject

[redacted]

8.2.4 Duration of Treatment per Subject

The duration of treatment is approximately 4 months per subject.

8.2.5 Treatment Compliance

At the beginning of the investigation, the site will receive device accountability forms to document how and when MRZF111 is dispensed to subjects or the MRZF111 kit is returned unused to the sponsor or destroyed on site. These forms will be made available to the authorized individuals (e.g., monitor, auditor) and include the following information: investigation number, dates, quantities, and the code number assigned to the MRZF111 kit and investigational subjects.

As the IMD will be injected by the investigator, treatment compliance of the subject is ensured. Dates of treatment need to be documented in the source documentation and the eCRF.

8.2.6 Treatment of Overdose

As treatment with the IMD is performed exclusively in a clinical setting under the supervision of trained medical personnel, the risk of overdose in this investigation is estimated to be low. [redacted] However, in the case an overdose occurred (i.e., over-correction), it must be recorded in the source documents and the IMD section of the eCRF and recorded as an AE. Any case of overdose leading to a SAE(s) must be reported to the sponsor in an expedited manner using the appropriate reporting form (see Section 10). Usually, overcorrection is an aesthetic issue and harmless for health. It resolves within six to 12 months without intervention. For the IMD used in this investigation, no antidote has been identified to date, and there is no known established therapy recommended for an overcorrection. The investigator is advised to use best clinical judgment in the unlikely event of an overcorrection with the IMD. Kadouch et al. [Kadouch 2017] recommend treating nodules resulting from overcorrection with massaging, aspiration, intralesional injection with sterile water or corticosteroids.

8.3 Previous and Concomitant Therapies/Procedures

After signature of informed consent and prior to randomization, the subject's medical history should include a detailed list of all medications (including rescue medication) and over-the-counter or prescription, oral or topical, anti-wrinkle or skin enhancer products (e.g., alpha hydroxyl acids, glycolic acids, skin-bleaching agents, retinol, or retinoic acids in the décolleté) the subject was taking for a period of at least 3 months previous to randomization. The record should include the drug name (trade or generic), route of administration (e.g., intravenous, oral), total daily dose/unit (expressed in mg, mL, or International Unit [IU]), indication, the start and stop date (day, month, and year) for each medication, and if the medication is ongoing at the end of the investigation.

Similar information should be collected and assessed for any non-drug therapies that may have an impact on investigational results, e.g., dermal treatments in the décolleté such as toxin treatments, ablative or fractional laser, microdermabrasion, microneedling, chemical peels, non-invasive skin tightening, implantation of non-permanent or permanent dermal fillers, surgical procedures (including implantation of ports, pacemakers or defibrillators and breast augmentation), regardless of time point before randomization.

The medical history including relevant non-drug therapies (as defined in the prior paragraph) have to be documented in the source documentation and the eCRF.

Local anesthetics, sedation or cooling applied prior to or after injection should be documented (please refer to the Section 8.1.3).

The following concomitant medications are forbidden during the investigation:

- During the whole course of the investigation:

- For ten days prior to and three days after treatment (applies to all injection cycles):

The following concomitant non-drug treatments are forbidden during the investigation:

- During the whole course of the investigation:

- For at least 24 hours after treatment (applies to all injection cycles):

[redacted]

- For at least 12 hours after treatment (applies to all injection cycles):

[redacted]

- At the day of a visit before assessments (applies to all visits):

[redacted]

Concomitant medication and concomitant non-drug treatments have to be documented in the source documentation and in the eCRF. This also applies to therapy changes (including changes of regimen) during the investigation.

8.4 Blinding Procedures

8.4.1 Blinding

[redacted] The identity of randomized and realized treatment group A or B will remain unknow [redacted].

8.4.2 Planned Unblinding Procedures

This is an open label study with [redacted] assessments of the effectiveness of the IMD. There is no planned procedure for unblinding foreseen in this study, and the [redacted] remain blinded until the end of the study.

8.4.3 Emergency Unblinding

This is an open label study and the treating investigator is unblinded. If a medical emergency occurs and a decision regarding the subject's condition requires knowledge of the number of treatment injection, the treating investigator may disclose to which treatment group the subject belongs.

9 INVESTIGATION ASSESSMENTS AND VISIT SCHEDULE

9.1 Clinical Evaluations

At the beginning of the investigation, the subject's medical history and all relevant current and concomitant medications, therapies and procedures planned during the investigation will be recorded (see Section 8.3) through oral investigation before any IMD injection. A review of this information will allow the investigator to assess whether the subject can be enrolled. Other data will be collected as required, including information obtained from physical examinations, weight, and height. If counseling of subjects is deemed necessary, either prior to enrollment or during the investigation, the following options will be made available: The investigator can refer to other specialists to clarify ambiguous results of the examination during screening period and during the whole course of the investigation.

9.2 Effectiveness Assessments

Any effort should be made that all assessments at the respective investigation site are performed by the same investigator or her/his designated and trained investigation site staff for all subjects enrolled at this site. [redacted] who is not delegated otherwise involved in this investigation and who is also not aware of the treatment regimen will perform the MAS endpoint assessments[redacted]. All assessments should be scored in individual subjects by the same rater throughout the investigation. However, if a second rater at the site is qualified, he/she is allowed to perform assessments in absence of the original rater. The name of the [redacted] has to be documented in the source data and eCRF.

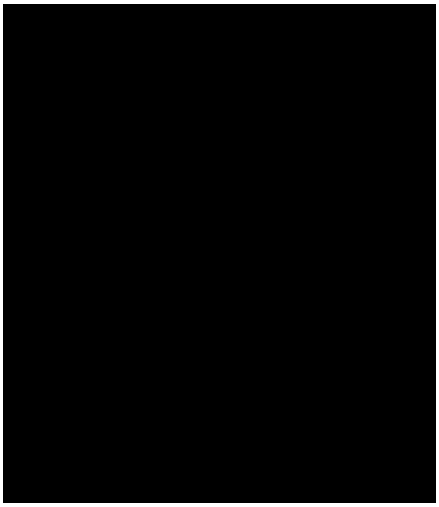
[redacted]

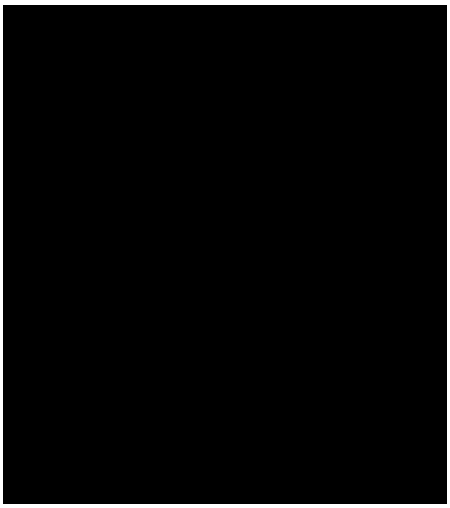
[redacted]

[redacted]

[redacted]

9.2.3 Biophysical Skin Quality Parameters





[redacted]

9.2.3.1 *Cutometer® dual MPA 580 – Skin Elasticity*

The Cutometer® is a standardized device to evaluate elasticity and other biomechanical parameters of the skin. By sucking the skin into the aperture of the probe, the elasticity (capacity of the skin to return in its original position) can be measured by using a non-contact optical measuring system.

[redacted]

The measurement of the Cutometer® curve (see Appendix 16.1) and the structure parameters will derive via Cutometer® software.

[redacted]

[redacted]

9.2.4 *Merz Aesthetics Scales for Décolleté Wrinkles*

For the décolleté area in women, two MAS were successfully created and validated for the assessment of the status of wrinkles, which are of importance for aesthetic treatment

procedures in this area [Landau 2016]. These two MAS (Décolleté Wrinkles-At Rest, Décolleté Wrinkles-Dynamic) [redacted] ill be used in this investigation. Thus, skin wrinkling is evaluated within the décolleté area in both at rest and dynamic positions.

The MAS **Décolleté Wrinkles-At Rest** will be used to assess the severity of wrinkles at rest (see Appendix 16.2).

The MAS **Décolleté Wrinkles-Dynamic** will be used to assess the severity of dynamic wrinkles (see Appendix 16.3).

9.2.5 Treatment Satisfaction Assessments

9.2.5.1 Subject's Treatment Satisfaction Assessment

Subjects will be queried on the level of subject treatment satisfaction (see Appendix 16.4) with the IMD treatment by being asked: "How satisfied or dissatisfied are you with the aesthetic appearance of your décolleté today? Please tick the one option that best fits."

If the subject responds "somewhat dissatisfied", "dissatisfied", or "very dissatisfied", he/she will be asked for additional explanation as to why he/she is not satisfied. Additional explanation, if any, will be kept within the source data and entered at a separate (from the scale) comment field on the eCRF.

9.2.5.2 Investigator's Treatment Satisfaction Assessment

Treating investigators will be queried on his level of treatment satisfaction (see Appendix 16.5) with the IMD treatment in the subject by being asked: "Based on your clinical experience, how satisfied or dissatisfied are you with the current aesthetic appearance of the subject's décolleté? Please tick the one option that best fits."

If the treating investigator responds "somewhat dissatisfied", "dissatisfied", or "very dissatisfied", he/she will be asked for additional explanation as to why he/she is not satisfied. Additional explanation, if any, will be kept within the source data and entered at a separate (from the scale) comment field on the eCRF.

9.2.6 Global Aesthetic Improvement Scales on Décolleté Wrinkles

9.2.6.1 Subject's Global Aesthetic Improvement Scale on Décolleté Wrinkles

The **sGAIS-Wrinkles** [redacted] will be used to assess aesthetic improvement in the subjects according to the subjects. [redacted]

[redacted]

9.2.6.2 *Investigator's Global Aesthetic Improvement Scale on Décolleté Wrinkles*

The **iGAIS-Wrinkles** [redacted] will be used to assess aesthetic improvement in the subjects according to the treating investigators [redacted]

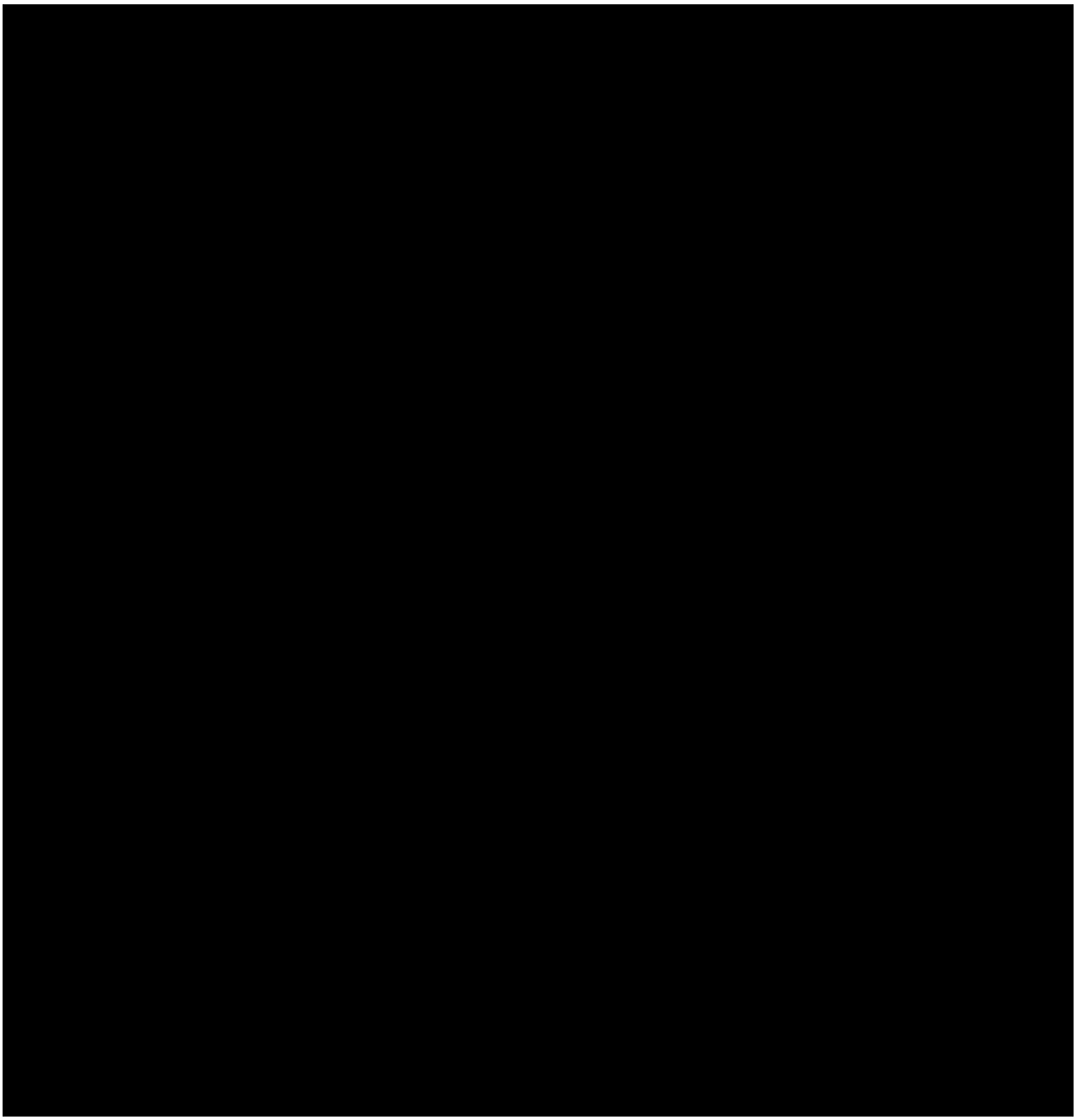
9.2.7 *Global Aesthetic Improvement Scales on Décolleté Skin Quality*

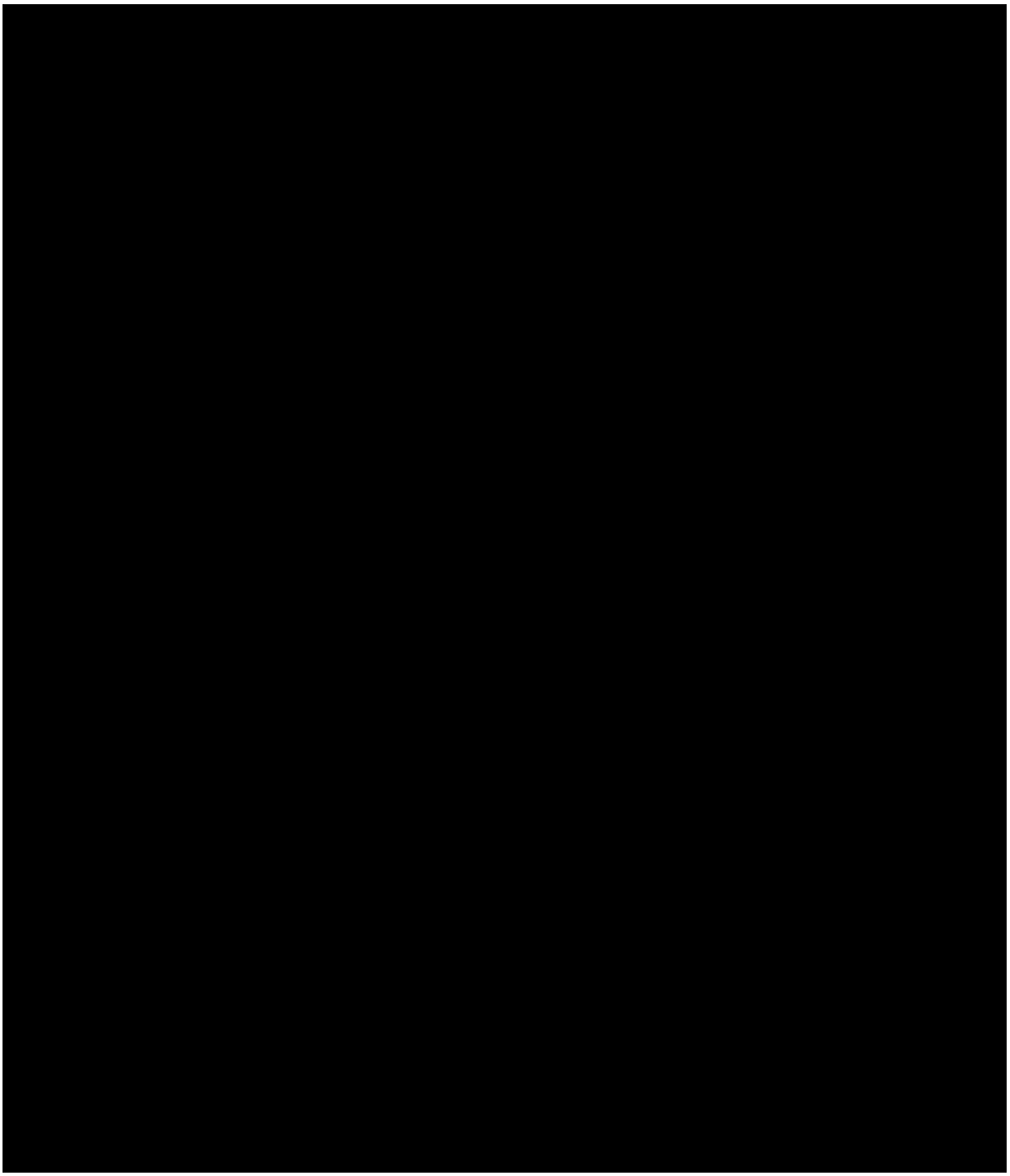
9.2.7.1 *Subject's Global Aesthetic Improvement Scale on Décolleté Skin Quality*

The **sGAIS-Skin Quality** [redacted] will be used to assess aesthetic appearance of skin quality improvement according to the subjects [redacted]

9.2.7.2 *Investigator's Global Aesthetic Improvement Scale on Décolleté Skin Quality*

The **iGAIS-Skin Quality** [redacted] will be used to assess aesthetic appearance of skin quality improvement in the subjects according to the treating investigators [redacted]





9.4 Laboratory Evaluations

A urine pregnancy dip stick test will be performed before each injection visit in women of childbearing potential[3]. For time points of this assessment please refer to Table 2.

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

9.5 Visit Schedule

The purpose of the baseline visit is to determine subject eligibility for investigation participation. Subjects who are diagnosed with a medical condition during the screening process will be notified and referred for medical care.

Baseline is defined as Day 1/V1 which is the day of enrollment, randomization (pre-injection) and first injection of the IMD.

Subjects will be randomized to either treatment group A or treatment group B.

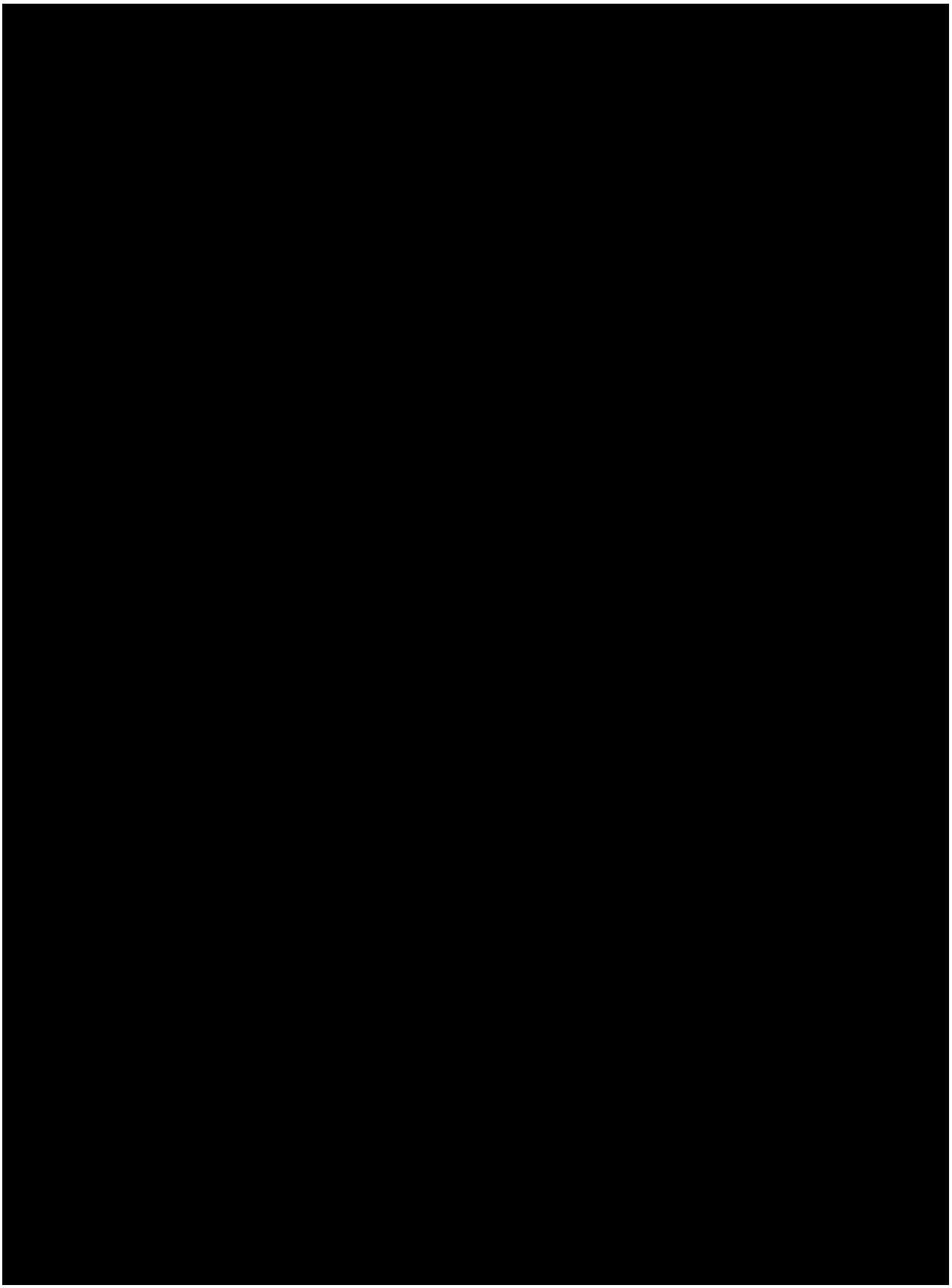
- Treatment group A is assigned to receiv [redacted].
- Treatment group B is assigned to receive [redacted]

[redacted]

Unscheduled visits may be required in the case of premature discontinuation of investigational treatment and have to be documented in the source data. 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 on-site, depending on the nature of the follow-up required.

Where a visit to the site is not possible within the allowed time frame due to COVID-19 public health emergency, safety related information (AEs, pregnancy, concomitant medications and concomitant non-drug treatment) should be gathered via telephone

preferably on or around the initially planned date for that visit. Study subjects need to provide prior verbal agreement to this procedure.



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 IMD.

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 investigational 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 IMD 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 IMD, must be documented, treated, and followed up like all other AEs.

[redacted]

TEAEs are defined as AEs with onset or worsening at or after the first injection of the IMD.

Pre-existing conditions noted in the medical history and previous to IMD injection 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.

In case of a positive COVID-19 result, the "COVID-19 infection" has to be documented as an AE in the eCRF. All individual symptoms related to the confirmed COVID-19 infection should be recorded as separate AEs attributable to COVID-19 using the following descriptions e.g. "cough due to confirmed COVID-19 infection".

10.1.2 Adverse Event Handling and Reporting

Data pertaining to AEs will be collected during the telephone contact 24 or at latest 48 hours after each IMD treatment and during each clinical investigation visit based on the subject's spontaneous description, through investigator inquiry, or discovered in the course of examinations done during the visit.

At each clinical investigation visit, the investigator will assess and record any AE in detail in the source data and on the eCRF AE report form. The following information must be recorded:

- AE diagnosis or main symptom;
- Location of AE: outside of injection area, (e.g. 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), date serious since and reason for seriousness;
- Outcome (see Section 10.1.5);
- AE leading to discontinuation of the clinical investigation (yes or no);
- Stop date.

If on-site visits are not possible due to COVID-19 pandemic and the subject provides his/her consent to safety assessments on the phone, safety assessments (AEs, change in medication and non-drug treatment, and occurrence of pregnancy) will be performed via phone calls and the results documented in the source data first and in the eCRF subsequently. For documentation requirements, please refer to section 11.2.

For all adverse events that are collected during telephone visits, it is up to the medical judgement of the investigator to refer a subject to a specialist if deemed necessary, thus ensuring the safety of the subject and the accuracy of the data.

For documentation of a COVID-19 positive test result see Section 10.1.1.

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

In case of an SAE (defined in section 10.2), the investigator must also complete an SAE report form and report it to Merz and 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 Investigational Medical Device

An AE is considered to be “related” to IMD or the injection procedure if a causal relationship between the IMD or the injection procedure and an AE is at least reasonably possible (i.e., the relationship cannot be ruled out). In this case the event is considered an ADE (see Section 10.3). If the event is serious it is a “serious ADE” (SADE) (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)

An SAE is an adverse event that:

a) led to death,

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

1) a life-threatening illness or injury, or

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

Based on MPSV the definition for a SAE additionally comprises any unintended event which occurred in the scope of the clinical investigation, and directly or indirectly led, might lead to or might have led to death or to a serious deterioration of the state of health of a subject, user or any other person regardless whether the event is related to the IMD.

10.2.1 Serious Adverse Event Details

In case of 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 Serious Adverse Events

All SAEs as well device deficiencies that could have led to a SADE (see section 10.6.1) [redacted] must be immediately reported preferably via e-mail and SAE report form to Merz and the CRO. The CRO will report the SAE to the sponsor including additional relevant documents. Further reporting details will be outlined in the Safety Management Plan.

Although all information required for completion of an SAE report form may not be available, 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:

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

[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 to the CRO 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 IMD.

As this clinical investigation is performed in Germany, Merz is responsible to report SAEs as well device deficiencies that could have led to a SADE [redacted] to the German Regulatory Authority BfArM based on §3 paragraph (5) of the current German Ordinance on the Medical Device Safety Plan (Medizinprodukte-Sicherheitsplanverordnung, MPSV).

In accordance with MPSV §5 paragraph (2), SAEs shall be reported to the BfArM immediately using the SAE reporting form for Germany if a causal relationship to the IMD cannot be ruled out. All other SAEs shall be documented completely and reported quarterly or upon request by the BfArM as summary using the MEDDEV 2.7/3 SAE report table. Furthermore, the SAE assessment form provided by the BfArM shall be used. Should no SAEs occur within a defined reporting period, a report shall nonetheless be submitted.

The address for SAE reporting to BfArM is MPSAE@bfarm.de.

In order to ensure reporting of SAEs immediately to the BfArM, the Medical Devices Safety Officer at Merz provides 24 hours availability.

A copy of submitted reports will be provided to the CRO for submission to EC and dissemination to all investigators.

In accordance with MPSV 14 paragraph (1,2), the sponsor and the investigator will take immediately all necessary safety measures to protect immediate or indirect danger in case that circumstances can affect the safety of the subjects, users or third parties. The Medical Devices Safety Officer at Merz will immediately inform the BfArM about these new circumstances and submit the information in addition to the responsible ethics committee.

10.3 Definition of an Adverse Device Effect (ADE)

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

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

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

10.4 Definition of a Serious Adverse Device Effect (SADE)

A SADE is defined as an ADE 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 anticipated SADE (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 unanticipated SADE (USADE) is a SADE 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 clinical investigation must be immediately reported by the investigator via pregnancy report form to the CRO. 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 IMD.

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 effectiveness.

NOTE Device deficiencies include malfunctions, use errors, and inadequate labeling.

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:

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 EC are possible at any time, even after the end of investigation. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit investigation-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, investigator meetings, monitoring, centralized evaluations, and validation methods).

This investigation will be monitored regularly by a qualified monitor from the CRO according to EN ISO 14155:2011 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 investigation should be retained in the respective source documentation (e.g., subject file/medical records). 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 and eligibility 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. Details to the injection treatment have to be entered in the source data [redacted]. 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, subject eDiary, questionnaires).
During the study period, the COVID-19 outbreak occurred. Subjects might get tested for SARS-CoV-2; however, this is not a general procedure foreseen in the study protocol. Nevertheless, according to national and international guidance documents, collection of specific information which might explain the basis for e.g. missing data, is important. Therefore, any relevant circumstances related to the COVID-19 outbreak should be documented in the source data, e.g. reason for visit not performed / visit performed via phone. A COVID-19 infection itself has to be documented as an adverse event. Corresponding documentation in the eCRF should be done as follows:

- In case of a positive COVID-19 result, the "COVID-19 infection" has to be documented as an AE in the eCRF. In case of symptoms related to the confirmed

COVID-19 infection, all individual symptoms should be recorded as separate AEs attributable to COVID-19 using the following descriptions e.g. “cough due to confirmed COVID-19 infection”.

- All changes to visits or premature terminations due to COVID-19 should be documented in the source data as well as in the eCRF.

- Visits not done regularly on site due to COVID-19 pandemic will be marked in eCRF as visit not done or done virtually via phone contact.

If an investigation site is using an electronic system for documenting source data, a member of the investigation 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 investigation 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 Site File or in the medical records (information must be visible that the subject was in a clinical investigation/investigation number). 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. Further details are described in the Monitoring Plan.

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 investigational subjects), then no such paper print-outs are required.

11.3 Data Management

Data required according to this CIP is to be recorded in the web-based eCRFs (electronic data capture system) provided by the CRO Metronomia.

All users who will enter data into the eCRF will be previously trained. The successful completion of the training of all participants will be documented in a listing, or participants will receive a training certificate, which will be a prerequisite for the access to the eCRF. The access to the eCRF is password-controlled and conforms with CFR part 11. Patient reported outcome data will be collected by a web based electronic data capture system called “Clincase ePRO” which is a separate module of the eCRF with write access restricted to the respective subject. All data collected from ePRO are synchronized in real time mode with the Clincase server via Internet (e.g. Wi-Fi, 3G). This means, that data are submitted directly to EDC and no local data are stored on the subjects’ own device (smartphone/tablet/computer). Subjects will get access to the ePRO web portal through personal invitation by investigator (personal web-link for registration). The access to the subject’s eDiary itself is password-controlled and requires a separate PIN. Investigators or the delegated site staff will have read only permissions to view the data of their respective subjects. This guarantees that subjects data entries cannot be changed.

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 investigation 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 investigation site staff) can be raised during source data verification, medical or safety review and data management review.

Validated systems are used for electronic data capture.

After all data are entered and all queries are solved, the database will be closed. In case of any changes to the data after database close, these changes will be documented according to the respective SOP. Further details are described in the Data Management Plan.

11.4 Monitoring

This investigation will be monitored regularly by a qualified monitor of the CRO according to EN ISO 14155:2011 (chap. 8.2.4) and the respective SOPs. During these visits, the monitor will prepare the investigation site for the conduct of the investigation, check for subject eligibility, for completion of the entries in the source data and on the eCRFs, including completeness and content of the patients' eDiaries; for compliance with the CIP, EN ISO 14155:2011, Declaration of Helsinki, and regulatory authority requirements; for the integrity and verification of the source data with the eCRF entries; and for subject eligibility. Monitoring will also be aimed at detecting any misconduct or fraud.

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

The investigator and all investigation site 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 IMDs dispensed in the eCRF and the device inventory records.

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

11.5 Auditing

Audits shall be conducted by qualified auditors to evaluate compliance with the CIP, sponsor's current written procedures, ISO14155:2011 and the applicable regulatory requirements. These audits may cover all involved parties, systems and facilities and are independent of, and separate from, routine monitoring or quality control functions.

An audit can be conducted:

a) as a routine part of the sponsor's quality assurance program,

b) to assess the conduct of the monitoring activity,

c) whenever there are serious or repeated CIP deviations or suspicion of fraud,

d) to bring an investigation site into "inspection readiness", i.e., to prepare the investigation site for a potential regulatory inspection, and

e) when requested or suggested by a regulatory authority.

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

12 STATISTICAL METHODS

This section describes the statistical analyses intended at the time of investigation planning. Further details on the statistical and analytical aspects will be presented in the 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 CIP or in the SAP. All deviations and/or alterations will be summarized in the clinical investigation report.

12.1 Determination of Sample Size

The primary effectiveness endpoint is the proportion of subjects with at least 1 point (≥ 1 point) improvement on the MAS Décolleté Wrinkles-At Rest scale at 16 weeks after last treatment compared to baseline (Day 1) [redacted]. By use of a one-sided binomial test, it will be tested at an error level of 2.5% whether the response rate is significantly larger than 50%. It is aimed to ensure a power of 90%. The binomial test is applied to the pooled data from both treatment groups. [redacted] To account for up to 10% drop-outs and potential exclusions from the FAS, a total of 112 subjects need to be enrolled in this study, i.e., 56 subjects need to be randomized to each treatment group. [redacted]

Per definition, the SES will be at least as large as the FAS. Thus, according to the above outlined assumptions, at least 100 subjects will be available for safety analyses. This sample size is sufficient to observe, with a probability of 80%, at least one adverse event with actual event probability of 1.6%.

With regard to safety analyses, it should be considered that the RADIESSE® in its original un-diluted form is marketed since 2003. Since then, over 5 million units had been sold and used in a variety of subject populations. In this period, the majority of reported AEs were common expected injection site reactions that were mild in nature and resolved over time. [redacted]

Consequently, the sample size for this study was primarily determined to ensure an adequate power for the primary effectiveness analysis, however, still providing a good probability of risk detection.

Calculations to determine the required sample size were performed using the software nQuery Version 8.1.2.0, Statistical Solutions Ltd. 2017, and validated by double programming with proc power on SAS 9.4, SAS Institute Inc., Cary, NC, USA, 2016.

12.2 Analysis Sets

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

Safety Evaluation Set

The SES is the subset of all randomized subjects who were exposed to the IMD at least once. Subjects will be analyzed as treated.

Full Analysis Set

The FAS is the subset of subjects in the SES for whom at least the baseline value of the primary effectiveness variable is available (i.e., all subjects who have a baseline value on the MAS Décolleté Wrinkles-At Rest scale). In contrast to the SES, subjects will be analyzed as randomized.

Modified Full Analysis Set

The modified FAS is the subset of subjects in the SES for whom at least the baseline value of the primary effectiveness variable is available (i.e., all subjects who have a baseline value on the MAS Décolleté Wrinkles-At Rest scale). Subjects will be analyzed as treated.

Per Protocol Set

The PPS is the subset of subjects in the modified FAS without major deviations. Subjects of treatment group A switching to treatment group B will be excluded from the PPS. Further major protocol deviations and other reasons leading to exclusion will be defined prior to database lock during a data review meeting.

12.3 Endpoints for Analysis

12.3.1 Effectiveness Endpoints

12.3.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the proportion of subjects with at least 1-point (≥ 1-point) improvement on the MAS Décolleté Wrinkles-At Rest scale at 16 weeks after last treatment compared to baseline (Day 1). [redacted] A response is defined as ≥ 1-point improvement on MAS Décolleté Wrinkles-At Rest scale at 16 weeks after treatment compared to baseline (Day 1).

12.3.1.2 Secondary Effectiveness Endpoints

- Proportion of subjects with at least 1-point (≥ 1-point) improvement on the MAS Décolleté Wrinkles-Dynamic scale at 16 weeks after last treatment compared to baseline (Day 1). [redacted] A response is defined as ≥ 1-point improvement on MAS Décolleté Wrinkles – Dynamic scale at 16 weeks after treatment compared to baseline (Day 1).

- Treating investigators treatment satisfaction assessment of aesthetic improvement in the subject after the décolleté treatments 16 weeks after last treatment.

- Subjects treatment satisfaction assessment of aesthetic improvement after the décolleté treatments 16 weeks after last treatment.

- Treating investigator's evaluation of the global aesthetic improvement on the iGAIS-Wrinkles from baseline (Day 1) [redacted] to 16 weeks after last treatment.

- Subject's evaluation of the global aesthetic improvement on the sGAIS-Wrinkles from baseline (Day 1) [redacted] to 16 weeks after last treatment.

[redacted]

[redacted]

12.3.2 Safety Endpoints

12.3.2.1 Secondary Safety Endpoints

- Incidence of TEAEs related to the treatment with the IMD.

[redacted]

[redacted]

12.4 Statistical Analysis Methods

[redacted]

12.4.1 Effectiveness Endpoints

The primary and secondary effectiveness endpoints will be summarized using the modified FAS population with missing data replaced as described in Section 12.4.4.1, for sensitivity purposes, these analyses will also be performed on the modified FAS with observed data and on the PPS. All remaining effectiveness endpoints will be summarized on the modified FAS population on observed data. Additional information related to the usage of the analysis populations as it relates to the statistical analyses of investigational results will be described in the SAP.

[redacted]tatistics will be provided for each endpoint for the pooled data and by realized treatment group. Metric variables will be summarized by number of observations, mean, standard deviation, min. median, max. Categorical variables will be summarized by number and rate of events per category where the denominator will be chosen according to the adequate analysis population. Ordered categorical data will be summarized by metric and categorical statistics. All variables will be analyzed as absolute data and as change from baseline, as applicable.

If not otherwise specified, confidence intervals in the following refer to two-sided 95% Wilson score confidence intervals.

All data captured in the eCRF will be listed.

12.4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from baseline to 16 weeks after last treatment as assessed by the blinded live rater.

The primary analysis will be based on a one sided binomial test at the one-sided type I error level of $\alpha = 0.025$ for the pooled data from both treatments against the null-hypothesis that the response rate is ≤50%:

H_0: R ≤50%

H_1: R >50%

As further supportive explorative analyses, the effectiveness for the different time points of treatments with a 16 weeks post-treatment period in both treatment groups will be analyzed as for the primary endpoint:

- Proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from last treatment application to 16 weeks after last treatment as assessed [redacted] in treatment group A.
- Proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from last treatment application to 16 weeks after last treatment as assessed [redacted] in treatment group B.
- Proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-At Rest from baseline to 16 weeks after first treatment as assessed [redacted] in treatment group B.

In addition, two-sided 95% Wilson score confidence intervals will be provided overall, and for each treatment group in the supportive analyses.

The primary effectiveness analyses will be based on the modified FAS [redacted] Sensitivity analyses of the primary endpoint will be provided based on observed cases only and on the observed cases in the PPS.

The supportive explorative analyses will be performed on the observed cases in the modified FAS as well as on observed cases in the FAS.

12.4.1.2 Secondary Effectiveness Endpoints

One secondary effectiveness endpoint is the proportion of responders (response rate) defined as subjects with ≥ 1-point improvement on the MAS Décolleté Wrinkles-Dynamic

from baseline to 16 weeks after last treatment as assessed [redacted]. Same analyses as for the primary endpoint will be performed on this endpoint.

Number and percentage of subjects with any level of treatment satisfaction of the aesthetic improvement in subject's décolleté at 16 weeks after last treatment assessed by investigator and subject will be calculated and the according 2-sided 95% confidence intervals for the percentage of subjects with any level of treatment satisfaction will be provided for the pooled treatments (overall).

Number and percentage of subjects with improvement in iGAIS-Wrinkles defined in a rating of 1, 2 or 3 at 16 weeks after last treatment will be summarized and 2-sided 95% confidence intervals be provided overall. Analogous methods will be used for sGAIS-Wrinkles.

[redacted]

[redacted]

12.4.2 Safety Endpoints

All safety analyses will be performed on the SES.

AEs will be coded according to the MedDRA version in effect at the time the database is closed. Only TEAEs will be analyzed, which are defined as AEs with onset on or after date of first injection of the IMD.

12.4.2.1 Secondary Safety Endpoints

Incidences of related TEAEs will be provided by SOC and PT.

[redacted]

[redacted]

12.4.4 Special Statistical/Analytical Issues

12.4.4.1 Handling of Discontinuations and Missing Data

Missing post baseline data for the primary endpoint will be imputed according to the underlying reasons for missingness [redacted]

12.4.4.2 Interim Analyses

Not applicable.

12.4.4.3 Data Monitoring Committee

Not applicable.

12.4.4.4 Multiple Comparisons/Multiplicity

The analysis of the primary effectiveness endpoint is planned to be performed on the pooled data from both treatment groups. Further tests on both treatment groups separately are to be considered as explorative supportive analyses. Therefore, the type one error rate has not to be adjusted.

13 DATA HANDLING AND RECORDKEEPING

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

13.1 Corrections to Data

All data required by this CIP are to be entered into a validated database of eCRFs. However, unless otherwise specified in Section 11.2, direct entries are not allowed; data must be transcribed from the source (e.g., subject file) to the eCRF.

If corrections in subject scales or assessments are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date and sign the correction. The investigator should not make any changes to these documents. The data management/biostatistics vendor (Metronomia Clinical Research GmbH) will be responsible for data processing. Database close will occur only after quality assurance procedures have been completed.

13.2 Recordkeeping

Essential documents should be retained for at least 15 years after the last date of manufacture. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by agreement with the sponsor.

The sponsor and principal investigator shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.

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

- Source documentation (e.g. subject files, medical records, [redacted] subject, investigator and [redacted] questionnaires).
- Subject identification code list (i.e., provided by template to the investigator, along with the Investigator Site File, at the beginning of the investigation), which identifies the subject by number, name, and date of birth.
- A signed copy of the final CIP and any amendment.
- CD/DVD/USB with eCRF data, data clarification forms, and any associated subject-related source data [redacted] or, where applicable, authorized copies of source data).
- Signed informed consent forms.
- Copies of site investigators' and co-workers' curricula vitae.
- Copies of all direct correspondence with the EC and with the regulatory authority (ies).

- Copies of IMD receipt forms and device inventory forms.
- Copies of all relevant correspondence between the investigator and the monitor, and between the investigator and the sponsor.
- Copies of safety information reported during the investigation and submitted by the sponsor.

13.3 Destruction of Investigation Documents

Investigation documents may not be destroyed by investigation site personnel prior to the retention period specified above without the prior written consent of the sponsor. The party who signed the investigator contract must inform the sponsor in due time if the principal investigator leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

14 PUBLICATION POLICY

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

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

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16 APPENDICES