1 TITLE PAGE

NCT04795622, redacted version v1.0, 16Jan2023

Evaluation of the Effectiveness and Safety of the Ulthera® DeepSEE® System for Treating Skin Laxity in the Lower Face and Submentum

Trial Identifier: M960101056

Version Date: 08-JUL-2021

Investigational Medical Device (Generic Name): Ulthera® DeepSEE® (DS) System

System Components and Specification:

	Control Unit with Integrated Touchscreen	Handpiece	Transducers		
			DS 10-1.5	DS 7-3.0	DS 7-4.5
Product Code Information:	UC-1	UH-2	UT-4	UT-1	UT-3

Indication: Improvement in skin laxity of the lower face and submentum

Category of Investigational Medical Device: Type III medical device that needs clinical trial approval Yes ☐ No ☒

Similar products in China Yes ☐ No ☒

Clinical Trial Institution: [redacted] China

Lead/Coordinating Investigator: [redacted]

Trial Design: Prospective, 180-day, randomized, multicenter, evaluator-blind, controlled trial

Sponsor: Ulthera, Inc.
a division of Merz North America, Inc.
[redacted]

Legal Agent Information: Merz Pharma China, Ltd.

Contract Research Organization: [redacted]

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

2 SYNOPSIS

Title of Trial	Evaluation of the effectiveness and safety of the Ulthera® DeepSEE® System for treating skin laxity in the lower face and submentum
Trial Identifier	M960101056
Investigative Sites	This trial will be conducted at approximately five investigative sites in China.
Investigational Medical Device (Generic Name)	Ulthera® DeepSEE® System
Indication	Improvement in skin laxity of the lower face and submentum.
Objectives	*Effectiveness:* Demonstrate superiority of treatment with the Ulthera DeepSEE System compared to untreated control for the improvement of skin laxity of the lower face and submental area. *Safety:* Demonstrate the safety of treatment with the Ulthera DeepSEE System for the improvement of skin laxity of the lower face and submental area.
Effectiveness Evaluation	*Primary endpoint* • Proportion of subjects with improvement in lower face and submental skin laxity at Day 9 [redacted] *Secondary endpoints* • Displacement of skin (mm) in the submentum at Day 90 [redacted]. • Proportion of subjects with any improvement [redacted] on the Investigator Global Aesthetic Improvement Scale (iGAIS) at Day 90 [redacted], as assessed by the treating investigator for the Treatment Group. • Proportion of subjects with any improvement [redacted] on the Subject Global Aesthetic Improvement Scale (sGAIS) at Day 90 [redacted], as assessed by the subjects in the Treatment Group. • Change from baseline in FACE-Q™ Satisfaction with Lower Face and Jawline score (Rasch-transformed) at Day 90, as assessed by the subjects in the Treatment Group.

Safety Evaluation	*Secondary endpoint* • Incidence of treatment emergent adverse events (TEAEs) related to the Ulthera DeepSEE System, as reported by the treating investigator throughout the trial.
Trial Design Overview and Methodology	This is a prospective, 180-day, randomized, multicenter, evaluator-blind, controlled trial designed to evaluate the effectiveness and safety of the Ulthera DeepSEE (DS) System for improving the appearance of skin laxity of the lower face and submentum. Subjects will be enrolled from participating investigative sites in China. A total of 200 subjects will be randomized 1:1 to either the Treatment Group or Control Group stratified by investigative site. The Treatment Group will receive a single treatment at Day 1 with the Ulthera DeepSEE System to the midface, lower face, submentum, and upper neck with three DS transducers (DS 10-1.5, DS 7-3.0, DS 7-4.5) and will be followed for 180 days after treatment. The Control Group will not receive treatment at Day 1 and will remain untreated until Day 90 (delayed treatment). Following completion of all protocol-mandated assessments at Day 90, the Control Group will receive a single treatment with the Ulthera DeepSEE System to the midface, lower face, submentum and upper neck with three DS transducers (DS 10-1.5, DS 7-3.0, DS 7-4.5) and will be followed for 90 days after treatment. For both the Treatment Group and Control Group, the starting energy level (EL) will be EL2 for the DS 10-1.5 transducer, and EL4 for the DS 7-3.0 and DS 7-4.5 transducers. [redacted] All subjects will participate in this trial for 180 days and will be evaluated at screening, Day 1, Day 90, and Day 180. Follow-up telephone calls will occur at 3 days and 14 days after treatment. Subjects in the trial will have a screening period up to 14 days and, once randomized, will participate for a maximum duration of 180 days (± 14 days).
Number of Trial Subjects	Approximately 250 subjects are planned for screening to allow for 200 subjects randomized in this study.
Main Inclusion/ Exclusion Criteria	*Select inclusion criteria are as follows:* • Healthy male or female aged 35 to 65 years at the time of screening; • Mild to moderate lower face and/or submental laxity that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention; [redacted]

	[redacted] *Select exclusion criteria are as follows:* • Scarring in area(s) to be treated; • Any active implants (e.g., pacemakers or defibrillators) in the area(s) to be treated; • Any metallic implants in area(s) to be treated; • Any open wounds or lesions in the area(s) to be treated; • Body mass index (BMI) less than 19 or greater than 30; or • Gain or loss of ≥ 2 BMI units within the previous 90 days or has the intention to gain or lose ≥ 2 BMI units during the course of the trial.

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ANOVA	Analysis of variance
AOI	Area of Interest
ASADE	Anticipated serious adverse device effect
BMI	Body mass index
CD	Compact disc
CFDA	China Food and Drug Administration
ChiCTR	Chinese Clinical Trial registry
Chinese GCP	China's Good Clinical Practice for Medical Devices
CI	Confidence interval
CMDE	Center of Medical Device Evaluation (China)
CRF	Case report form
CRO	Contract research organization
CTP	Clinical trial protocol
[redacted]	
DS	DeepSEE
DVD	Digital versatile disc
eCRF	Electronic case report form
EDC	Electronic data capture
EL	Energy Level
EN ISO	International Organization for Standardization (ISO) as adopted by the European Union (EN)
EOT	End of trial
EU	European Union
FACE-Q™	Set of subject-reported outcome scales
FAS	Full analysis set
[redacted]	
FDA	Food and Drug Administration (USA)
FSFV	First subject, first visit

Abbreviation	Definition
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
ICF	Informed consent form
IEC	Independent ethics committee
IFU	Instructions for use
iGAIS	Investigator Global Aesthetic Improvement Scale
IMD	Investigational medical device
IRB	Institutional Review Board
[redacted]	
LS	Least squares
LSLV	Last subject, last visit
MedDRA	Medical Dictionary for Regulatory Activities
MFU	Microfocused ultrasound
MFU-V	Microfocused ultrasound with visualization
NHFPC	National Health and Family Planning Commission of the People's Republic of China
NMPA	National Medical Products Administration (China)
[redacted]	
PEV	Primary endpoint visit
PHI	Protected health information
PPS	Per protocol set
[redacted]	
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software®
SES	Safety evaluation set
sGAIS	Subject Global Aesthetic Improvement Scale

Abbreviation	Definition
SOC	System organ class
SOP	Standard operating procedure
TCP	Thermal coagulation point
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UADE	Unanticipated serious adverse device effect
USA	United States of America
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet

Definitions of Terms

Synonymous terms		
Clinical trial protocol	=	Clinical investigation plan
Effectiveness	=	Clinical performance
Investigational medical device	=	Investigational device or Investigational product
Trial	=	Investigation or study

Sponsor and Investigator Information

Sponsor Information

Sponsor Name	Ulthera, Inc. a division of Merz North America, Inc.
Sponsor Address and Contact Information	Ulthera, Inc. 1840 South Stapley Drive, Suite 200 Mesa, Arizona 85204, USA Phone: [redacted] Merz North America, Inc. 6501 Six Forks Road, Raleigh, North Carolina 27615 USA Phone: [redacted]
Agency Name, Address, Contact Information, and Qualified Documents Related	Merz Pharma China, Ltd. Room 608, Tomson Financial Building, 710 Dong Fang Road, Shanghai, China, 200122 Phone: [redacted]

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

Clinical Trial Institution Name	[redacted]
Huashan Hospital Affiliated to Fudan University	
Peking University First Hospital	
Air Force General Hospital, PLA Dermatology Department	
Shanghai Ninth People's Hospital	
Beijing Hospital	

Responsibilities of All Parties

Sponsor's Statement

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

Investigator's Statement

I agree that:

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

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

Comments from the sponsor:

Signature (stamp):

Date (MM/DD/YYYY):

Comments from the investigator:

Signature (stamp):

Date (MM/DD/YYYY):

Comments from the medical device clinical trial institution:

Signature (stamp):

Date (MM/DD/YYYY):

5 ETHICS

5.1 Ethical Conduct of the Trial

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

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

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

5.2 Informed Consent

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

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

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

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

5.3 Subject Privacy

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

[redacted]

5.4 Confidentiality of Subject Information

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

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

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

5.5 Insurance

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

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

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

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

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

5.6 Financing

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

6 INTRODUCTION

6.1 Background

Many factors contribute to the natural aging process during which an individual's skin gradually loses its youthful appearance. Aging skin is characterized by loss of volume, decreased elasticity, and increased laxity. Clinical attempts to reverse or slow the aging process have employed a variety of aesthetic techniques. Long considered the gold standard, rhytidectomy is an effective, long-term solution for improving aesthetics of the aging face. However, more recently, there has been a focus on achieving skin tightening and soft tissue lift, approximating that of a surgical facelift, without the associated possible complications or extended recovery.[1]

The facial rejuvenation market is rapidly advancing to accommodate the growing demand for such methods of skin lifting and tightening.[2] As a result, many products and procedures have been developed to treat facial rhytids and skin laxity. Traditional ablative chemical peels and dermabrasion were among the original approaches to improving fine lines and wrinkles.[3] The development of full-face laser ablation treatments followed [4], but their use has been limited by potential side effects and extended recovery time.[5] Microneedling has also been introduced to improve the signs of skin aging, but this technique requires multiple sequential treatments, and it may take up to one year to achieve noticeable results.[6]

Various energy-delivery devices have also been developed, and are designed to create thermal injury to stimulate fibroblast proliferation and collagen synthesis (e.g., fractionated ablative lasers, radiofrequency devices, fractional infrared devices).[7] However, most energy-based devices only produce tightening effects within superficial layers of the skin. Microfocused ultrasound (MFU) energy can provide deeper skin-tightening effects by focusing energy deposition in the dermis and subcutaneous tissue. Compared to epidermal treatments, ultrasound-energy use is associated with fewer adverse post-treatment effects as it can penetrate to deeper layers of skin and leave the epidermal layers and intervening skin tissues relatively unaffected.[8]

The Ulthera® System is a non-invasive, dermatological, aesthetic treatment that is cleared by the United States Food and Drug Administration (FDA) to lift the eyebrow (FDA 510(K) number: K072505), lift (K121700) and improve the appearance (K180623) of lax submental and neck tissue, and reduce wrinkles and lines in the décolleté (K134032). In previous clinical trials, the Ulthera System has demonstrated safety and effectiveness as a non-invasive aesthetic treatment. The Ulthera System utilizes MFU energy with visualization (MFU-V) to create thermal coagulation points (TCPs) in the deep reticular layer of the dermis and sub-dermis while leaving the epidermal layers and overlying papillary dermis unaffected.[9] These thermal microinjuries lead to collagen scaffold remodeling that lifts the overlying skin and tightens the dermal layers.[9, 10] Under the current FDA clearance, DeepSEE® transducers are used in combination with the Ulthera System to incorporate high-resolution ultrasound imaging with MFU therapy. With a tissue

image depth of 8 mm, using this ultrasonic visualization enables operator avoidance of ultrasound-energy contact with large neurovascular structures and bone.

6.2 Trial Rationale

Patients seeking aesthetic treatments are frequently concerned about the appearance of the lower face and submentum consequent to skin and soft tissue laxity.[11] Sagging or laxity in the submental area can occur with aging, specifically as a result of decreased elasticity, increased skin redundancy, and fat accumulation.[12] The Ulthera DeepSEE System treats lax tissue in the mid- and lower face, submental area, and upper neck and offers a non-invasive approach to improving the aesthetic appearance in the submental region and jawline. The Ulthera DeepSEE System, which has been on the market in the USA since 2009, is currently available in > 70 countries, with approximately 1.5 million procedures performed worldwide to date (data on file).

6.2.1 Justification of Proposed Trial Design and Primary Effectiveness Endpoint

The current trial is designed to demonstrate the effectiveness and safety of the Ulthera DeepSEE System for treatment of the mid- and lower face, submental area, and upper neck to tighten skin and lift and improve the appearance of lax submental (beneath the chin) and neck tissue. Subjects with mild to moderate lower face and/or submental laxity that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention will be treated. Subjects will receive one treatment with the Ulthera DeepSEE System to the midface, lower face, submentum, and upper neck tissue using three Ulthera DeepSEE transducers with a treatment map that aligns with clinical best practice guidelines.

The primary effectiveness endpoint has been chosen to demonstrate that treatment with the Ulthera DeepSEE System is superior to untreated control through the detection of clinical improvement in submental and lower face skin laxity in post-treatment [redacted] at Day 90 [redacted].

See Section 8.2 for additional discussion on the trial design.

6.3 Potential Benefits and Risks

The potential benefit of treatment with the Ulthera DeepSEE System is lifting and improvement in skin laxity of the lower face and submentum. By delivering treatment at specific depths, Ulthera improves the superficial appearance of fine lines and wrinkles in

the skin as well as the overall appearance of the lower face and submentum by lifting the deeper soft tissue planes.

Potential treatment site responses associated with the use of the Ulthera DeepSEE System reported in previous clinical trials of the Ulthera DeepSEE System include: erythema (redness), edema (swelling), welting (localized area of linear visible edema), momentary pain/discomfort during the procedure while energy is being deposited, post-procedure discomfort, tenderness to touch, bruising, transient nerve effects (e.g., numbness due to inflammation of a sensory nerve, pain, paresthesia, tingling, itching), and transient local muscle weakness due to inflammation of a motor nerve. The possibility for burns, which may or may not result in permanent scar formation, may occur if incorrect treatment technique is used (e.g., tilting transducer, incorrect line spacing, gel pockets). Some scars may respond to medical treatment and resolve fully.

Adverse events (AE) have been reported in post-market surveillance following the commercialization of the Ulthera DeepSEE System. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the Ulthera DeepSEE System. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to the Ulthera DeepSEE System: pain, burns or burning sensation, edema / swelling, nodules, bruising, fat / volume loss, neuropathy, numbness, paresthesia, palsy, paresis, speech difficulty, muscle weakness, headache, migraine, visual change, skin sagging / drooping, asymmetry, erythema, welts, hives, rash urticaria, pruritis, blistering, scarring, discoloration, and hyperpigmentation.

[redacted]

Risks will be minimized or reduced by monitoring the subject during treatment, with careful observation of the subject's pain and skin response to treatment. Previous clinical trials with the Ulthera DeepSEE System have shown the sensory response was tolerable from both the subject's and investigator's perspective.[9] If a case arises whereby the treatment is not tolerated, the treating investigator has the option to reduce transducer energy level to improve treatment tolerability. If treatment tolerability is not improved following energy level reduction, the treating investigator may utilize additional measures to improve tolerability as described in Section 10.5.1.2. If treatment remains intolerable following the implementation of these measures, the treating investigator must stop administering treatment for the subject's safety, and the subject will be followed for AEs throughout the trial duration.

7 TRIAL OBJECTIVES AND ENDPOINTS

7.1 Objective

Effectiveness

- Demonstrate superiority of treatment with the Ulthera DeepSEE System compared to untreated control for the improvement of skin laxity of the lower face and submental area.

Safety

- Demonstrate the safety of treatment with the Ulthera DeepSEE System for the improvement of skin laxity of the lower face and submental area.

7.2 Endpoints

7.2.1 Effectiveness Endpoints

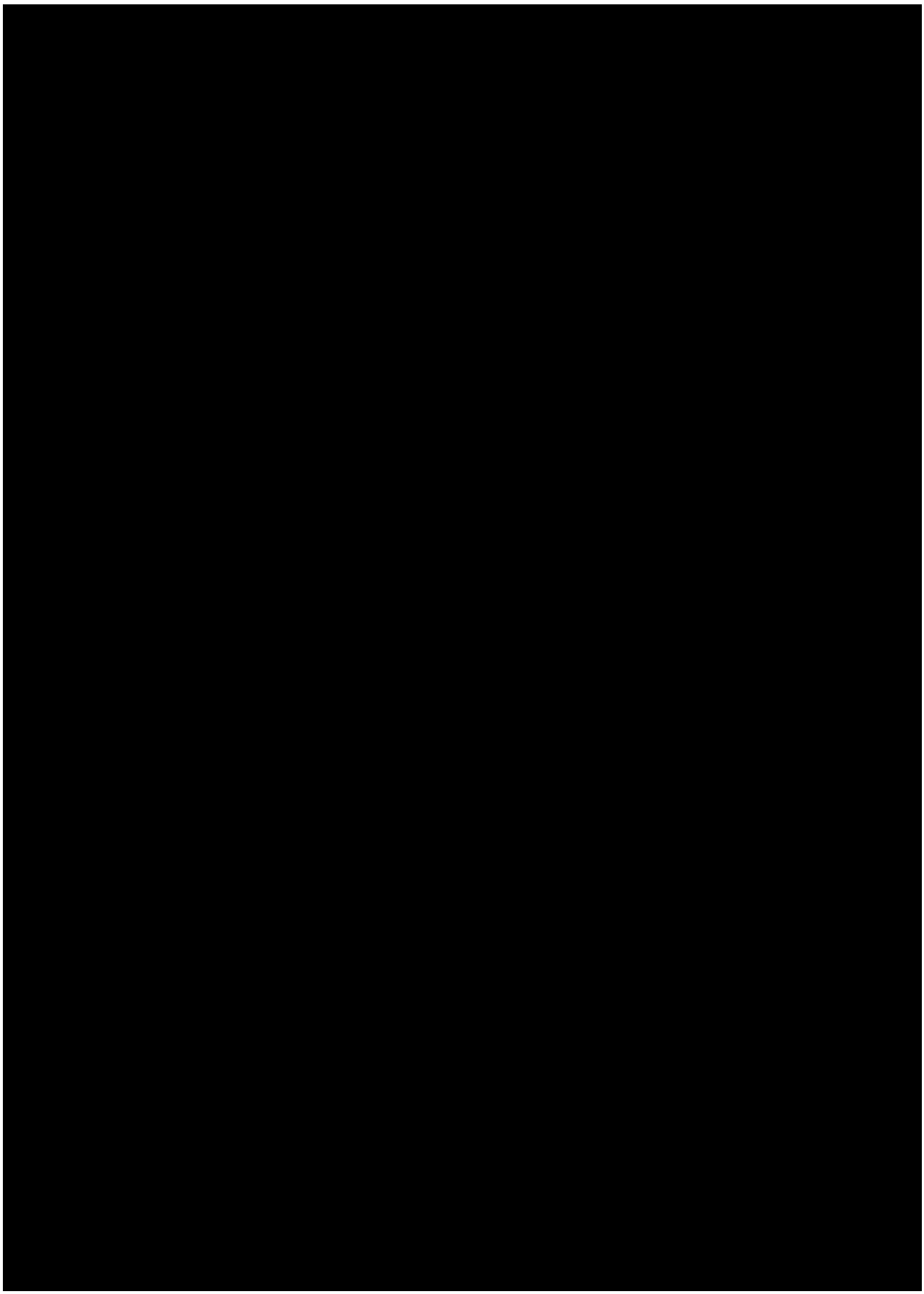
Effectiveness will be analyzed for the Treatment Group and Control Group as specified below. [redacted]

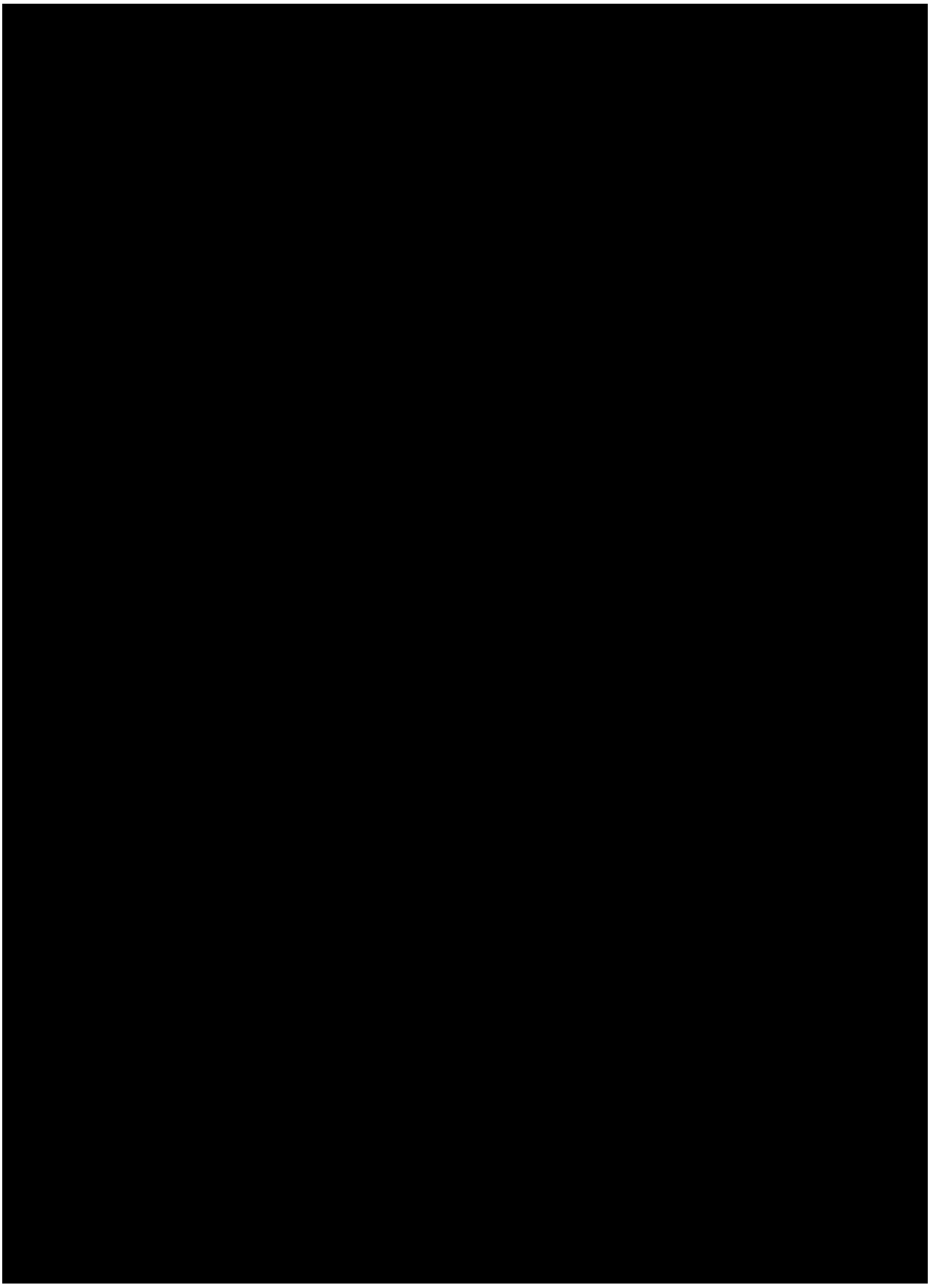
7.2.1.1 Primary Effectiveness Endpoint

- Proportion of subjects with improvement in lower face and submental skin laxity at Day 90 [redacted]

7.2.1.2 Secondary Effectiveness Endpoints

- Displacement of skin (mm) in the submentum at Day 9 [redacted]
- Proportion of subjects with any improvement [redacted] on the Investigator Global Aesthetic Improvement Scale (iGAIS) at Day 90 [redacted], as assessed by the treating investigator for the Treatment Group.
- Proportion of subjects with any improvement [redacted] on the Subject Global Aesthetic Improvement Scale (sGAIS) at Day 90 [redacted], as assessed by the subjects in the Treatment Group.
- Change from baseline in FACE-Q™ Satisfaction with Lower Face and Jawline score (Rasch-transformed) at Day 90, as assessed by the subjects in the Treatment Group.





7.2.2 Safety Endpoints

7.2.2.1 Secondary Safety Endpoint

- Incidence of treatment emergent adverse events (TEAEs) related to the Ulthera DeepSEE System, as reported by the treating investigator throughout the trial.

8 CLINICAL INVESTIGATION PLAN

8.1 Overview of Trial Design

This is a prospective, 180-day, randomized, multicenter, evaluator-blind, controlled trial designed to evaluate the effectiveness and safety of the Ulthera DeepSEE System for improving the appearance of skin laxity of the lower face and submentum. Eligible subjects will be healthy male or female subjects (35 to 65 years of age at time of screening) with mild to moderate lower face and/or submental laxity that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention.

[redacted] all investigators will be trained prior to trial start to identify subjects with trial-appropriate lower face and/or submental laxity. Each investigative site will also receive extensive training on the use of the Ulthera DeepSEE System prior to subject enrollment. Following completion of all training activities at each investigative site, approximately the first five subjects as selected by the investigator for potential enrollment and randomization will be confirmed for trial-appropriate lower face and/or submental laxity [redacted] during the screening period. Eligible subjects will be randomized 1:1 to treatment with the Ulthera DeepSEE System at Day 1 (Treatment Group) or to untreated control followed by delayed treatment with the Ulthera DeepSEE System at Day 90 (Control Group). Randomization will be stratified by investigative site.

At Day 1, the Treatment Group will receive a single treatment with the Ulthera DeepSEE System to the midface, lower face, submentum, and upper neck with three DS transducers (DS 10-1.5, DS 7-3.0, DS 7-4.5) and will be followed for 180 days after treatment. The Control Group will not receive treatment at Day 1 and will remain untreated until Day 90 (delayed treatment). Following completion of all protocol-mandated assessments at Day 90, the Control Group will receive a single treatment with the Ulthera DeepSEE System to the midface, lower face, submentum, and upper neck with three DS transducers (DS 10-1.5, DS 7-3.0, DS 7-4.5) and will be followed for 90 days after treatment.

For both the Treatment Group and Control Group, the starting energy level (EL) will be EL2 for the DS 10-1.5 transducer, and EL4 for the DS 7-3.0 and DS 7-4.5 transducers. [redacted]

The Treatment Group will be evaluated at Day 1 (treatment), at 3 days and 14 days post-treatment (phone calls for safety only), Day 90, and Day 180. The Control Group will be evaluated at Day 1, Day 90 (delayed treatment after effectiveness assessments), at 3 days and 14 days post-treatment (phone calls for safety only), and Day 180 (90 days post-treatment).

The primary effectiveness endpoint, the proportion of subjects with improvement in lower face and submental laxity (Section 7.2.1.1), will be assessed for both trial groups at Day 90 [redacted]

[redacted]. Standard safety parameters, including documentation of AEs and SAEs, will be assessed. [redacted] fter a maximum 14-day screening period, the planned trial duration for individual subjects is 180 days (± 14 days).

[redacted]

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

As detailed in Section 8.1, this is a prospective, multicenter, randomized, evaluator-blind, controlled trial. The trial will be conducted at approximately five sites to improve data homogenization and to minimize site-associated biases. This multicenter design approach will also increase the representativeness of the trial results. Randomization will eliminate selection bias in treatment assignment.

Since no approved, marketed, directly comparable products are currently available in China for treatment of lower face and submental laxity, an untreated Control Group will be used for the primary effectiveness assessment in this trial. To maximize the number of subjects exposed to acquire adequate safety data, subjects in the Control Group will receive delayed treatment with the Ulthera DeepSEE System at Day 90 upon completion of all effectiveness assessments.

The trial duration of 180 days represents a reasonable timeframe to assess effectiveness as well as delayed-onset and/or long-term AEs. A single treatment protocol using three transducers targeting specific tissue depths at a variable energy level was chosen based on published results. Those studies indicate effectiveness for the majority of subjects and capture of any potential AEs at 90 days following treatment.[2, 8, 9] Following the Treatment Group until Day 180 ensures capture of any late responders to treatment as well as potential delayed-onset or long-term AEs.

Ulthera DeepSEE treatment maps used in this trial (Section 10.5.1.3) represent a safe standard for treatment of the lower face and submentum based on the consensus guidelines.[13] As recommended by the consensus guideline, for the majority of individuals, use of the DS 10-1.5 and DS 7-3.0 transducers are appropriate for treatment of the mid-to-deep reticular layer of the dermis and subdermis, whereas the DS 7-3.0 and DS 7-4.5 transducers are utilized to target the deeper facial planes such as the superficial musculoaponeurotic system and platysma, dependent on individual anatomy and the aesthetic subunit being treated. Pre-treatment visualization of the tissue depths in each subject is used to preclude treatment at the level of large neurovascular structures or bone.

The MFU energy levels are initially set at what are generally considered the highest tolerable levels, and will be titrated as needed for subject comfort, based on the consensus guidelines. It is accepted best practice to provide treatment at multiple energy levels at the discretion of the treating provider, without comprising results by maintaining the proper treatment line density.[13]

9 TRIAL POPULATION AND RESTRICTIONS

9.1 Number of Subjects and Sites

Assuming a screen failure rate of 20%, approximately 250 subjects are planned for screening. Of these, a total of 200 subjects will be randomized at approximately five investigative sites in China. Enrolled subjects will sign and date the ICF before any trial-related procedures are undertaken. At each of the investigative sites, the number of subjects randomized should not exceed 60 to ensure a reasonable distribution of subjects across all investigative sites.

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

Additional information regarding the estimation of sample size is reported in Section 13.1. Further information related to subject randomization is provided in Section 13.2.

9.2 Selection of Subject Population

Assessment for eligibility criteria is based on the subject's medical records, an interview with the candidate subject, and investigator judgment. Selection criteria have been chosen to identify a suitable and representative subject population to investigate the trial objectives and to minimize safety concerns in this population. All investigators will be trained prior to trial start to identify subjects with trial-appropriate lower face and/or submental laxity [redacted].

Following completion of all training activities at each investigative site, approximately five subjects as selected by the investigator for potential enrollment and randomization will be confirmed for trial-appropriate lower face and/or submental laxity [redacted] during the screening period.

9.2.1 Inclusion Criteria

To be eligible for trial participation, each subject must meet all of the following criteria at screening (Day – 14 to – 3; Visit 1 [V1]) and Day 1 (V2):

[redacted]

Healthy male or female aged 35 to 65 years at the time of screening.

Has mild to moderate lower face and/or submental laxity that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention.

[redacted]

[redacted]

9.2.2 Exclusion Criteria

Subjects meeting any of the following criteria at screening (Day – 14 to – 3; V1) and Day 1 (V2) are not eligible to participate in the trial:

[redacted]

- Scarring in area(s) to be treated.
- Any active implants (e.g., pacemakers or defibrillators) in the area(s) to be treated
- Any metallic implants in area(s) to be treated.
- Any open wounds or lesions [redacted], in the area(s) to be treated.

[redacted]

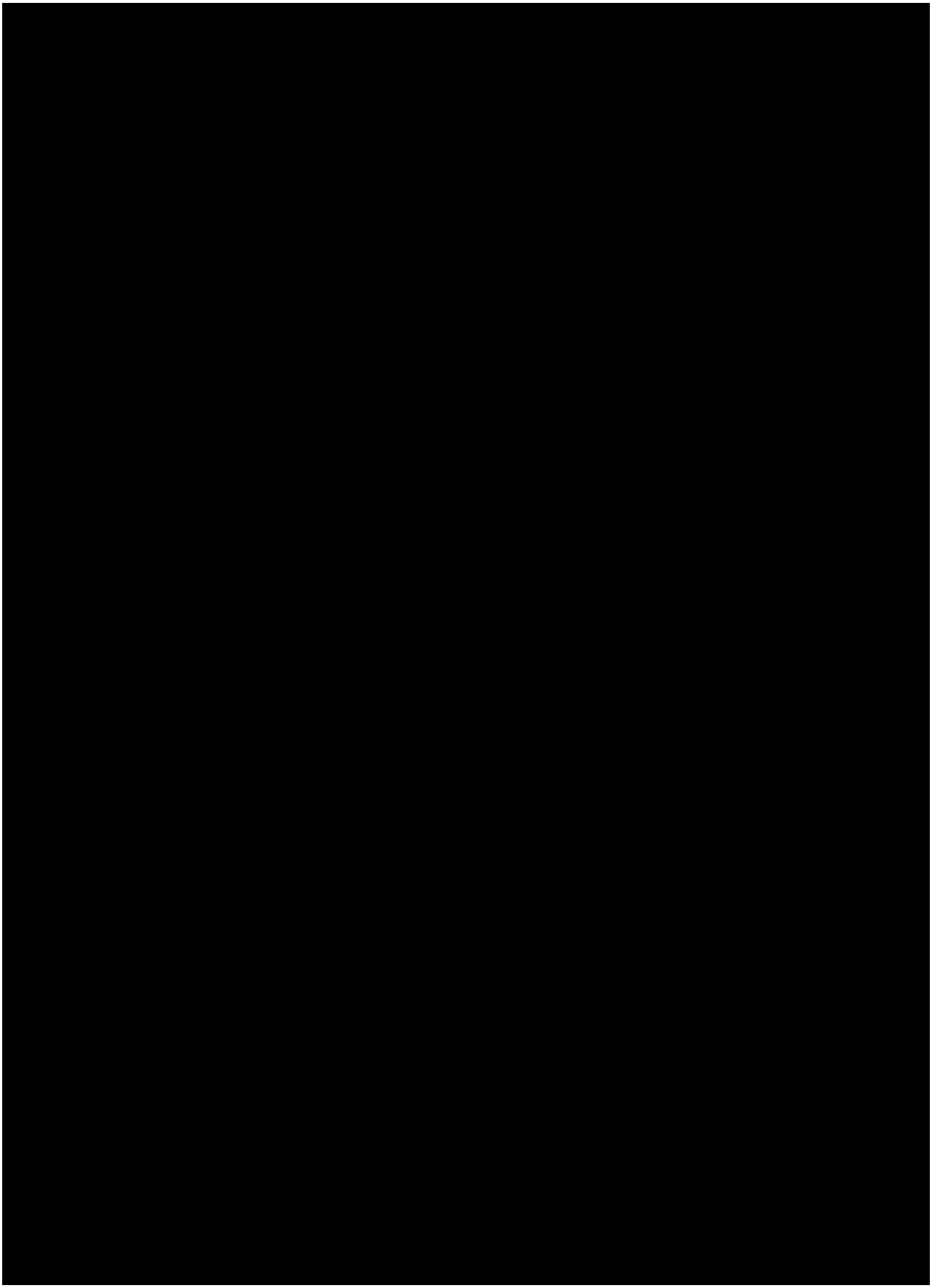
[redacted]

Body mass index (BMI) less than 19 or greater than 30.

Gain or loss of ≥ 2 BMI units within the previous 90 days or has the intention to gain or lose ≥ 2 BMI units during the course of the trial.

[redacted]

[redacted]



[redacted]

9.2.4 Subject Enrollment and Randomization

Subjects are considered to be enrolled once the ICF is signed and dated. Eligible subjects will be randomized during the screening period (Day – 14 to – 3). Randomization assignment will not be disclosed to the subjects until Visit 2 (Day 1).

Screen failures are defined in Section 9.2.5.

9.2.5 Screen Failures

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

9.2.6 Removal of Subjects from Therapy or Assessment

9.2.6.1 Treatment Discontinuation

If trial treatment is discontinued during administration, the investigator will record the reason for treatment discontinuation in the trial records. If the subject experiences escalating pain or discomfort during treatment with the Ulthera DeepSEE System that is not adequately controlled, the investigator may reduce transducer energy level to improve treatment tolerability (see Section 10.5.1.3). If subject pain or discomfort is not improved by energy level reduction, the investigator may use his/her discretion to suspend treatment to allow for additional pain management measures (see Section 10.5.1.2). Attempts should be made to optimize pain medication so that treatment can be completed.

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

9.2.6.2 Subject Withdrawal or Discontinuation

Each subject will be followed to the end of trial (EOT), or until the sponsor decides to terminate the trial, whichever comes first. The only reasons a subject will not be followed

for all scheduled visits include withdrawal of consent, continuous noncompliance with protocol requirements, or loss to follow-up (e.g., moving away from trial site; unresponsive to attempts to contact the subject). Additionally, the investigator can discontinue any subject, at any time, if medically necessary.

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

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

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

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

If a non-serious AE is unresolved at the time of the subject's final trial visit, an effort will be made to follow the subject until the AE is resolved or stabilized, the subject is lost to follow-up, or some other resolution of the event occurs. The investigator should make every attempt to follow all SAEs/unanticipated serious adverse device effects (USADEs) to resolution. [redacted]

9.2.6.3 Provision of Care for Subjects after Trial Discontinuation

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

9.2.7 Suspension or Premature Termination of an Investigative Site

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

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

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

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

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

9.2.8 Suspension or Premature Termination of the Trial

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

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

- Anticipated benefit cannot justify the risk;
- New scientific data do not justify a continuation of the trial;
- Determination of a potential safety risk to subjects;

- Inadequate subject enrollment;
- Decision by the regulatory authority or IEC/IRB to suspend or terminate approval/ favorable opinion for the trial; and/or
- Sponsor decision.

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

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

9.2.9 End of Trial

The end of the trial is defined as when the last subject completes the last visit.

10 TRIAL DEVICE AND TREATMENT OF SUBJECTS

10.1 Description of Trial Device

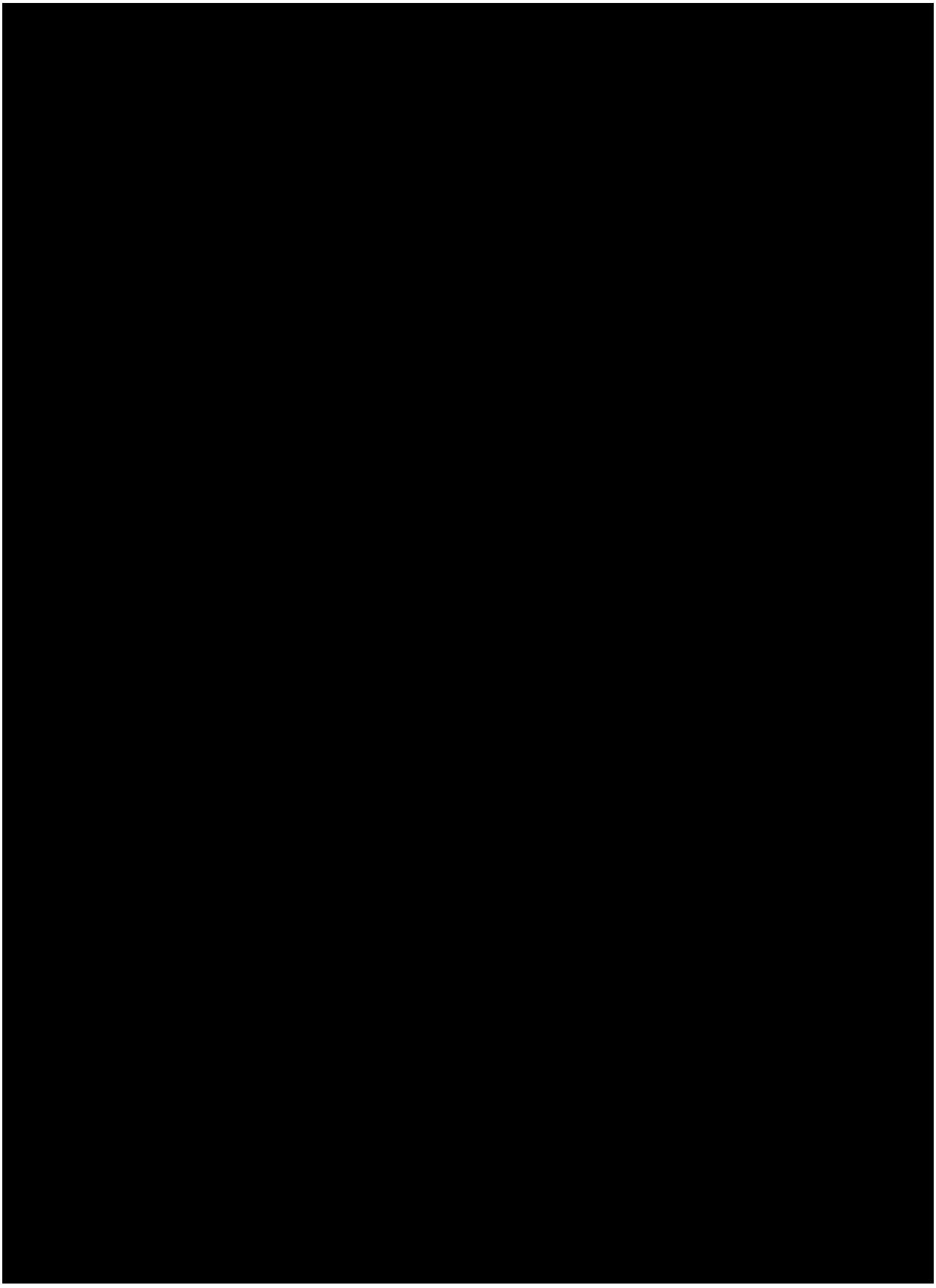
The Ulthera DeepSEE System is intended for lifting and sculpting of skin through deposition of ultrasound energy at depths between 1.5 and 4.5 mm beneath the skin surface. In the current study, the intended use of the Ulthera DeepSEE System is for improvement in skin laxity of the lower face and submentum.

The Ulthera DeepSEE System integrates the capabilities of ultrasound imaging with those of MFU therapy. The imaging feature, using the DeepSEE transducer, allows the user to visualize the dermal and subdermal regions of interest before treatment. This imaging feature enables users to ensure proper transducer coupling with the skin and adequate delivery of treatment energy at desired depths, avoiding structures such as bone.

The therapy feature directs highly focused, low energy (< 3 J) ultrasound waves to a specific tissue depth (mid to deep reticular dermis and sub-dermis) in the treatment area, sparing deeper tissues and the overlying epidermis. This controlled deposition of ultrasound energy heats the tissue and produces a line of discretely-spaced, thermal coagulation points (TCPs) at a specific treatment depth. This line of TCPs is also known as a treatment line. The end effect of the produced TCPs is the initiation of a tissue healing response (i.e., increased collagen and elastin synthesis), producing lift and tightening of skin.

A diagram of the Ulthera DeepSEE System is provided in Figure 1, consisting of three primary components: the control unit, the transducer, and the handpiece.

For this trial, the Ulthera DeepSEE System will be supplied by Ulthera, Inc. (Mesa, Arizona, USA) and marked for trial-specific clinical use. The sponsor will also provide a cart on which the Ulthera DeepSEE System will be placed, complete with drawers for storage of the transducers. [redacted]



10.3 Methods of Assigning Subjects to Trial Groups

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

- Treatment Group: Treatment with the Ulthera DeepSEE System at Day 1; or
- Control Group: Untreated control, with delayed treatment at Day 90.

Trial group assignments will be made based on the trial randomization scheme. A randomization list block-stratified by site will be created by a validated computerized randomization program. This randomization list will be uploaded to an electronic system that will allocate trial group assignment to the subjects in the eCRF according to the randomization list, if all relevant data were entered and the subject is eligible for participation in this trial. Randomized subjects will receive a unique randomization number, which will be recorded along with the date of randomization in the eCRF.

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

Additional details regarding randomization are provided in Section 13.2.

10.4 Blinding Procedures

10.4.1 Blinding

In this prospective trial, the treating investigators and subjects will not be blinded to trial treatment. For the primary effectiveness endpoint only (proportion of subjects with improvement in lower face and submental skin laxity; see Section 7.2.1.1), the [redacted] blinded evaluators will be blinded to trial group assignment. [redacted]

10.4.2 Planned Unblinding

Planned unblinding procedures are not necessary in the current trial design, as the treating investigator, trial coordinator, sponsor staff, and other trial personnel [redacted] are not blinded to trial group assignments.

[redacted]

10.5 Trial Treatment

All protocol-specific criteria for the administration of trial treatment must be met and documented prior to administration of any trial treatment. All treatments with the Ulthera DeepSEE System will be performed onsite by the treating investigator; subjects will not be dispensed any investigational material. Any noncompliant investigative site may be discontinued from the trial (Section 9.2.7).

[redacted]

10.5.1 Planned Treatment Procedure and Administration

10.5.1.1 Pre-treatment Assessments

All subject-related, pre-treatment activities (Section 11.1[redacted]) should be completed prior to administration of pre-treatment medications.

[redacted]

[redacted]

10.5.1.3 Treatment Regions and Treatment Administration Procedure

The skin of the midface, lower face, submentum (beneath the chin), and upper neck will be treated as described in Table 3 with three Ulthera DeepSEE transducers:

- DS 7-4.5: 7 MHz, 4.5 mm focal depth
- DS 7-3.0: 7 MHz, 3.0 mm focal depth
- DS 10-1.5: 10 MHz, 1.5 mm focal depth

[redacted]

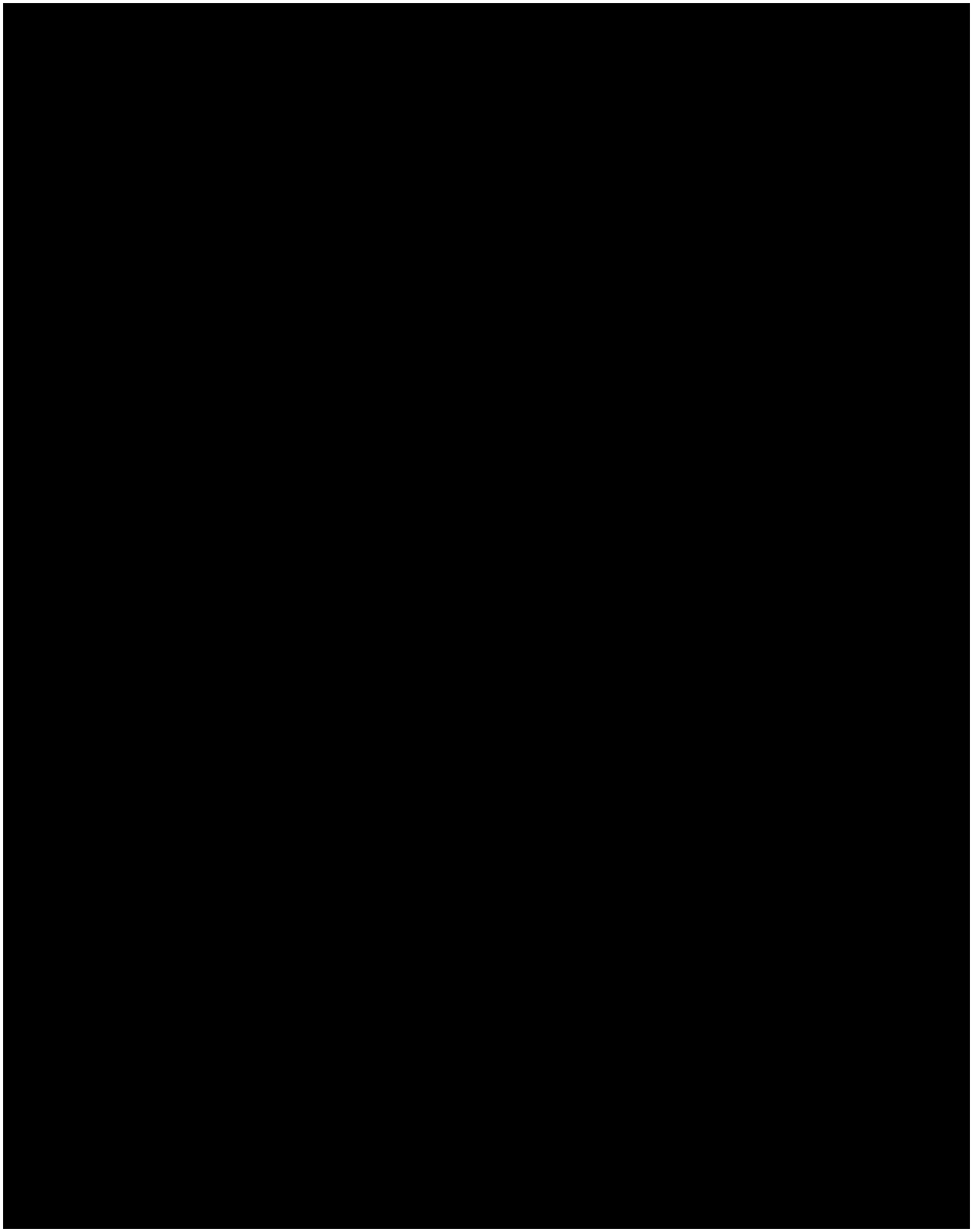
All investigators will be trained by the sponsor to use the Ulthera DeepSEE System ultrasound imaging to ensure that proper treatment is delivered (e.g., transducer contact, depth).

For the mid and lower face, treatment lines should be administered starting with the DS 7-4.5 transducer, followed next by the DS 7-3.0 transducer, and then by the DS 10-1.5 transducer. For the submentum (underneath chin) and neck, treatment lines should be administered starting with the DS 7-3.0 transducer, followed next by the DS 10-1.5 transducer. [redacted]

Overall, a total of 820 treatment lines are planned for administration. At the discretion of the treating investigator, subjects may receive up to 10% additional treatment lines, concordant with variations of individual subject anatomy such as increased surface area within the treatment region. However, the treating investigator should ensure that the additional treatment lines are delivered in a symmetrical fashion. For example, if additional treatment lines are delivered to the Right Mid/Lower Face region, approximately the same number of additional treatment lines should be delivered in the Left Mid/Lower Face region.

[redacted]

[redacted]



10.5.2 Selection and Timing of Treatment for Each Subject

Subjects in the Treatment Group will receive a single treatment with the Ulthera DeepSEE System at Day 1 (V2). Subjects in the Control Group will not receive treatment at Day 1 and will remain untreated until Day 90 (V3). Following completion of all protocol-mandated assessments at Day 90 (Section 11.1 [redacted]), the Control Group will receive a single treatment with the Ulthera DeepSEE System.

10.5.3 Treatment Interruption and Modification

If any problems occur during system operation, the treating investigator should take the following immediate action(s): lift the transducer off the subject's skin, press the **See** button on the handle to discontinue treatment in progress, and/or press the red emergency **Stop** button to completely halt system operation.

[redacted]

10.6 Prior and Concomitant Therapy

Medical history and concomitant therapy that is deemed relevant for study conduct by the investigator (e.g., chronic diseases, previous aesthetic treatments) should be documented in the eCRF. Restrictions regarding concomitant therapy are discussed in detail in Section 9.2.2 (Exclusion Criteria) and Section 9.2.3 (Restrictions during the Trial).

10.7 Trial Supplies and Packaging of Treatment Supplies

The sponsor will provide the Ulthera DeepSEE System including console, handpiece, and transducers. This investigational medical device (IMD) is to be used exclusively for treatment of subjects enrolled in this trial and will be labeled as follows: "CAUTION - Investigational Device. Limited to Investigational Use Only." Device labels will also note the sponsor name and address, manufacturer name and address, study number, the quantity within the package, and any other required information (if applicable). [redacted]

Sites will also be supplied with trial-specific ultrasound gel, cleanser for washing of the treatment area, 3D facial camera system (Section 11.2.1.2), and a standardized hand mirror for use during the FACE-Q and sGAIS assessments. Clinical trial supply should be stored in a controlled area with limited access and stored separately from any commercial supplies.

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

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

10.8 Receipt, Storage, Dispensing, and Return

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

All trial devices must be stored in a secure area.

After the last subject has received treatment, and after verification of device accountability, it is the investigator's responsibility to return all used and unused IMD equipment (i.e., console, handpiece, and transducers) to the local depot. Appropriate records of return must be maintained for accountability purposes.

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

10.9 Device Accountability Procedures

All necessary trial supplies will be released to the investigator before site initiation at the latest. Accountability for trial supplies at the trial site is the responsibility of the investigator.

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

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

- The names of all persons who received or used each device.
- The date or dates of use and time.
- Subject identification.
- Date of return of used, unused, expired, or malfunctioning IMDs (if applicable).

Dispensing records (i.e., treatment lines administered, and energy levels used) are recorded on the subject's treatment record, which is automatically generated by the Ulthera DeepSEE System. These data will be transferred to the EDC system. An overall accountability log will be maintained for each subject, documenting the number of treatment lines administered as well as energy levels used in each treatment region.

All used and unused IMD equipment must be returned to the local depot immediately after the trial is completed (Section 10.8). Products destroyed during shipment or at an investigative site should be accounted for and documented. All clinical supplies must be accounted for at the termination of the trial and a written explanation provided for discrepancies.

10.10 Treatment Compliance

All treatments will be administered by the primary treating investigator or designated back-up treating investigators; therefore, assessment of compliance is unnecessary. Variations from the defined trial-treatment administration will be reported as protocol deviations.

10.11 Duration of Trial

Subjects will have a screening period up to 14 days and participate for a maximum duration of 180 days (± 14 days) after treatment.

The estimated trial duration from first subject, first visit (FSFV) to last subject, last visit (LSLV) will be approximately 15 months, including an estimated 9 months for subject recruitment to complete. The actual duration of the study will be calculated according to the actual date of the Clinical Study Report stamp.

11 TRIAL PROCEDURES

11.1 Visit Schedule

The investigation activities and visit schedule are detailed in the Schedule of Events [redacted].

The screening visit (V1) is required to determine subject eligibility for trial participation; this visit must be completed − 14 to − 3 days prior to Day 1 (V2). Eligible subjects will be randomized during the screening period (Day – 14 to – 3) to either the Treatment Group or Control Group.

At Day 1, the Treatment Group will receive a single treatment with the Ulthera DeepSEE System to the midface, lower face, submentum, and upper neck with three DS transducers (DS 10-1.5, DS 7-3.0, DS 7-4.5). The Control Group will not receive treatment at Day 1, and will remain untreated until Day 90. Following completion of all protocol-mandated assessments at Day 90, the Control Group will receive a single treatment with the Ulthera DeepSEE System to the midface, lower face, submentum and upper neck with three DS transducers (DS 10-1.5, DS 7-3.0, DS 7-4.5).

All treatments should be administered at the investigative site by the primary treating investigator or designated back-up treating investigators, occurring only after completion of all required pre-treatment procedures and assessments. [redacted]

[redacted]

Following treatment with the Ulthera DeepSEE System, subjects will be observed for a minimum of 30 minutes. Subjects in both trial groups will be contacted by telephone at 3 days (± 1 day) and 14 days (± 3 days) after treatment and will have an unscheduled visit if necessary due to safety concerns (Section 11.1.2).

[redacted]

Safety follow-up will occur until Day 180 ± 14 days (V4) for both trial groups, corresponding to 180 days post-treatment for the Treatment Group and 90 days post-treatment for the Control Group.

The primary endpoint visit will occur at Day 90 (± 7 days) post-treatment, and the EOT visit will occur at Day 180 (± 14 days). In the case of a subject's premature discontinuation of the trial, a final assessment (EOT visit) should be performed.

11.1.1 Scheduled Visits

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

11.1.2 Unscheduled Visits

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

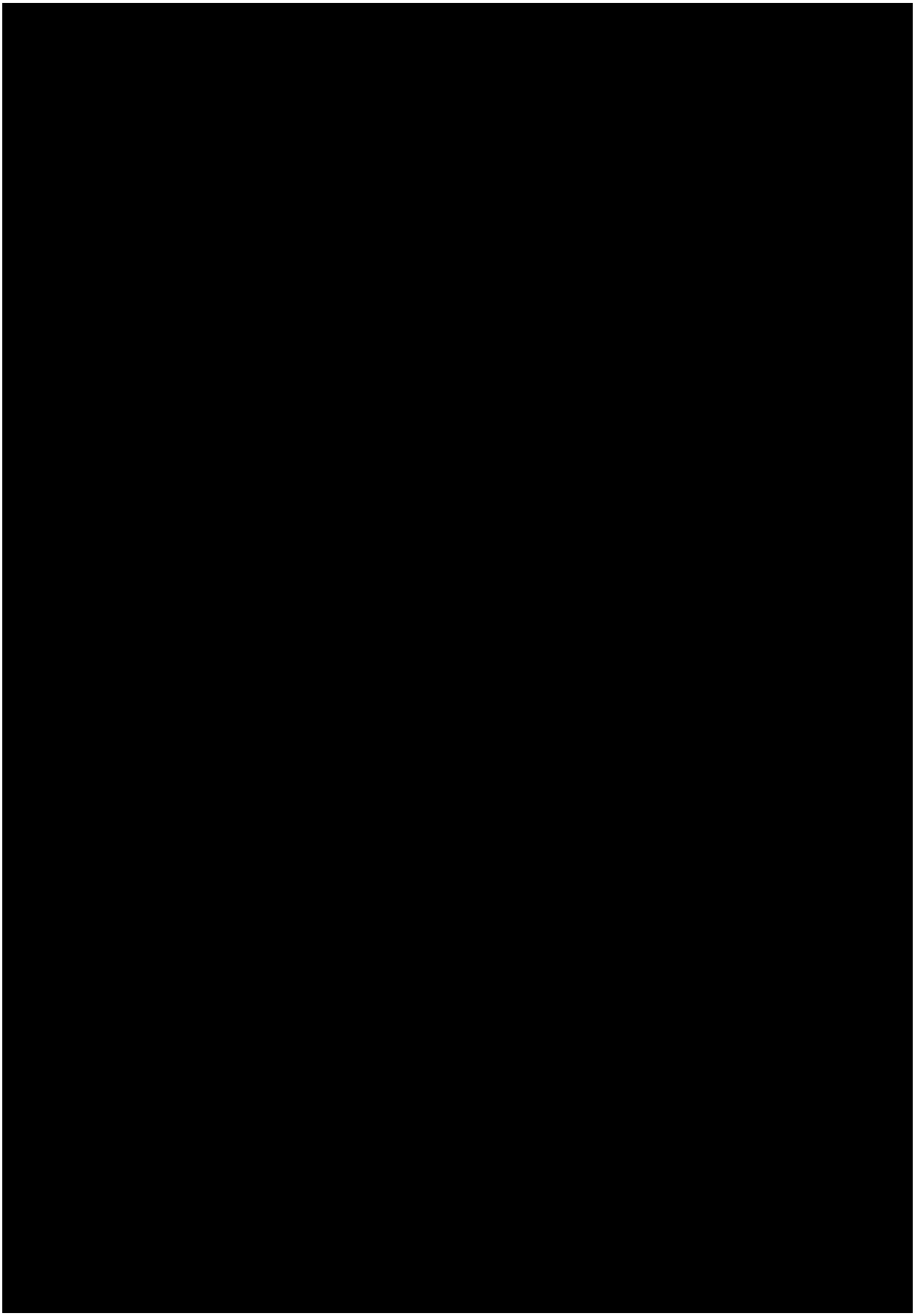
An unscheduled visit must be scheduled if information acquired from a subject during a post-treatment phone call, [redacted] requires additional follow-up as determined by the investigator.

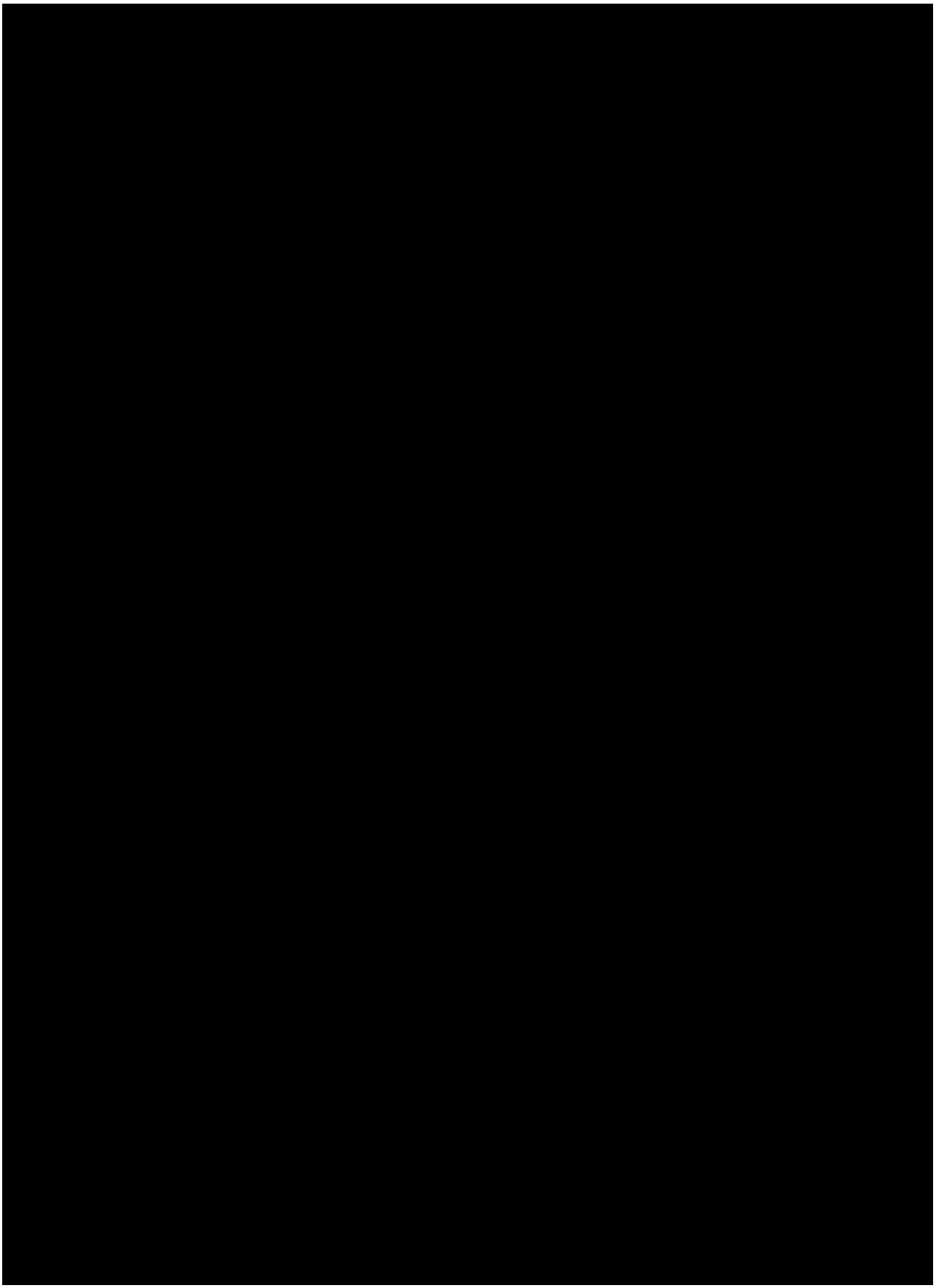
11.2 Trial Assessments and Definitions

11.2.1 Effectiveness Assessments

The effectiveness the Ulthera DeepSEE System for the treatment of skin laxity in the lower face and submental area will be evaluated using several assessments. Refer to the respective endpoints (Section 7.2), visit schedule (Section 11.1 [redacted]), and Schedule of Events [redacted] for additional information on the methods and timing of effectiveness assessments.

[redacted]





[redacted]

11.2.1.4 FACE-Q Assessment

FACE-Q is a set of validated, standardized patient-reported outcome scales for subjects receiving facial cosmetic procedures. [14-16] In this trial, subjects will evaluate treatment outcomes using the FACE-Q Satisfaction with Lower Face and Jawline instrument [redacted]. Subjects will utilize a mirror when answering the FACE-Q questionnaire. Standardized mirrors will be provided to sites to ensure subjects are utilizing the same type of mirror (i.e., standard size, shape, etc.).

For each subject, a sum score (range: 5 to 20) will be calculated; higher scores indicate a better outcome. Sum scores will then be Rasch-transformed (range: 0 to 100)[redacted]

[redacted]

11.2.1.5 Subject Global Aesthetic Improvement Scale (sGAIS)

Subjects will self-report using the sGAIS (Appendix 16.5.1) to assess overall aesthetic improvement of the lower face, submentum, and neck [redacted]. If a subject responds "no change", "worse", "much worse", or "very much worse" via sGAIS assessment, they will be asked to explain their choice of rating.

For completion of the sGAIS, subjects will use the same standardized mirror provided for FACE-Q assessment.

[redacted]

11.2.1.6 Treating Investigator Global Aesthetic Improvement Scale (iGAIS)

Treating investigators will use the iGAIS [redacted] to assess overall aesthetic improvement of the lower face, submentum, and neck [redacted].

[redacted]

11.2.2 Safety Assessments

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

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

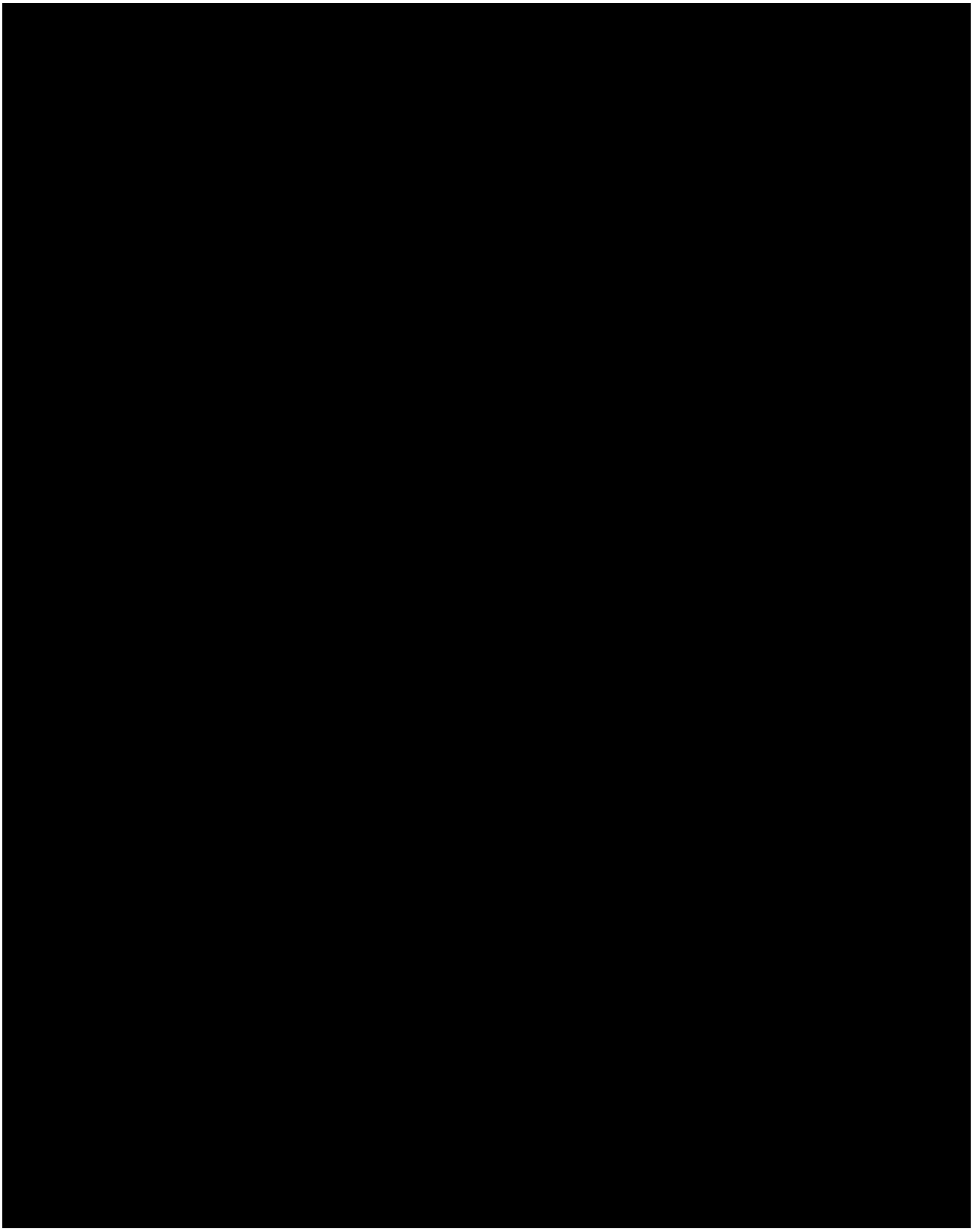
11.2.2.1 Adverse Events (AEs) / Serious Adverse Events (SAEs)

All AEs/SAEs reported by trial subjects, investigators, or other trial personnel after the time of informed consent through the EOT Visit (V4) will be recorded. All AEs/SAEs will be recorded regardless of causality. Additional information (e.g., definitions, reporting requirements) is provided in Section 12. All AEs/SAEs will be assessed throughout the trial, including on-site trial visits and during follow-up phone calls.

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

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

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



11.2.3 Additional Data Collected

Data for other assessments will be collected as follows:

- Demographics and other baseline characteristics, including height and weight;
- Dispensing records (i.e., treatment lines administered, and energy levels used);

[redacted]

- Relevant medical history/concomitant diseases;
- Concomitant medications and non-drug treatments; and
- Vital signs.

[redacted]

11.2.3.2 Vital Signs

Vital signs will be measured on all subjects after they have been seated for approximately five minutes. Resting heart rate and blood pressure (systolic and diastolic, preferably on the same arm each time) will be measured at screening (V1) and at the End of Trial Visit (V4).

[redacted]

11.2.4 Appropriateness of Assessments

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

12 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

12.1 Definition of an Adverse Event (AE)

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

Note:

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

12.1.1 Details of an AE

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

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

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

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

12.1.2 Reporting and Handling of an AE

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

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

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

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

12.1.3 Severity Grading for an AE

The clinical severity (i.e., intensity) of an AE will be classified as:

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

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

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

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

12.1.4 Causal Relationship of an AE with an Investigational Medical Device

An AE is considered to be "related" to IMD or to the treatment procedure if a causal relationship between the IMD or the treatment procedure and an AE is at least reasonably possible (i.e., the relationship cannot be ruled out). In this case, the non-serious event is

considered an "adverse device effect" (Section 12.3). If the event is serious, it is a "serious adverse device effect" (Section 12.4).

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

12.1.5 Outcome Categories for an AE

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

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

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

12.2 Definition of a Serious Adverse Event (SAE)

An SAE is an adverse event that:

a) led to death;

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

   1) a life-threatening illness or injury, or

   2) a permanent impairment of a body structure or a body function including chronic diseases, or

   3) inpatient or prolonged hospitalization, or

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

c) led to fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CTP, without serious deterioration in health, is not considered an SAE.

12.2.1 Details of an SAE

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

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

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

a) suitable action had not been taken; or

b) intervention had not been made; or

c) if circumstances had been less fortunate

should be categorized as an SAE and reported accordingly.

12.2.2 Reporting and Handling of an SAE

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

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

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

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

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

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

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

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

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

12.3 Definition of an Adverse Device Effect (ADE)

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

Note:

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

12.4 Definition of a Serious Adverse Device Effect (SADE)

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

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

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

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

A USADE is defined as follows:

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

12.5 Reporting of Pregnancy

Any pregnancy that starts during the clinical trial must be reported by the investigator to the sponsor and CRO immediately. Pregnancies and pregnancy follow-up should be reported on a Pregnancy Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the IMD. In addition, each pregnancy has to be reported on the AE eCRF page (i.e., as a non-serious AE due to device exposure before or during

pregnancy). Pregnancy Forms (including any follow-up forms) should be submitted to the contacts referenced in Section 12.2.2.

If a subject becomes pregnant during the trial, the subject must not receive treatment (i.e., delayed treatment for subjects in the Control Group); however, the subject will remain in the trial.

12.7 Definition of Device Deficiency

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

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

12.7.1 Reporting and Handling of Device Deficiencies

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

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

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

For reporting of device deficiencies:

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

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

MERZ	**CRO**
Merz North America – Product Surveillance 13900 W Grandview Parkway Sturtevant, WI 53177 USA [redacted]	[redacted]

As listed above, Merz North America – Product Surveillance will decide if the device needs to be returned and to whom the device should be sent for investigation.

13 STATISTICAL METHODS

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

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

13.2 Randomization

Each subject screened will be given a screening number. Only the subjects who are randomized will receive a randomization number during the screening period (Day – 14 to – 3). Subjects are randomized balanced (1:1) to one of the following groups:

- Treatment Group: Treatment with the Ulthera DeepSEE System at Day 1; or
- Control Group: Untreated control, with delayed treatment at Day 90.

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

See Section 10.3 for additional details on randomization.

13.3 Populations for Analysis

The following analysis sets will be defined:

- The randomized set is defined as all subjects randomized into the trial;
- The Safety Evaluation Set (SES) is defined as all subjects treated;

- The Full analysis Set (FAS) is defined as all subjects randomized [redacted]. Subjects randomized to the Treatment Group must also finish the treatment;
- The Per Protocol Set (PPS) is the subset of subjects in the FAS who have no major protocol deviations potentially biasing the statistical analysis of the primary endpoint. Final determination of what constitutes major or minor protocol deviations in this sense will be made prior to database close.

13.4 Analysis of Trial Data

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

Adequate descriptive statistics will be provided for all endpoints. In the following, metric descriptive statistics will comprise n, mean, standard deviation, median, quartiles, minimum, and maximum. Frequency tables for qualitative endpoints/variables will display absolute and percent frequencies (n, %). For both classes of statistics, confidence intervals might be added where deemed appropriate.

If not otherwise specified, statistical tests will be conducted two-sided at type I error rate 5%, and confidence intervals (CIs) will be two-sided with confidence level 95%.

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

13.4.1 Effectiveness Analyses

If not otherwise specified, effectiveness analyses will be based on observed cases in the FAS. For the FAS, all subjects will be analyzed as randomized.

13.4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined in Section 7.2.1.1.

Primary Analysis

The primary analysis of the primary effectiveness endpoint is conducted by using a logistic regression model with fixed effects treatment group and site. Analysis population will be the FAS. [redacted]
Effectiveness of treatment is confirmed if the p-value of the test is ≤ 5% and the odds ratio is in favor of Treatment (i.e., > 1).

[redacted]

Sensitivity Analyses

The following sensitivity analyses will be conducted to support the primary analysis:

1. Observed cases: the same approach as outlined for the primary analysis will be applied to observed cases instead of multiple imputation.
2. PPS: the observed cases analysis will be applied to the PPS.
3. Site effect [redacted].
4. Randomized set: the same approach as outlined for the primary analysis will be applied to all subjects in the randomized set [redacted].

13.4.1.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are defined in Section 7.2.1.2.

Displacement in skin in the submentum at Day 90 will be analyzed by applying an ANOVA [redacted] with fixed effects treatment group and site. The variance matrix among treatment groups will be left unspecified to allow for potential heterogeneous variances. Denominator degrees of freedom will be approximated by the Satterthwaite method. The ESTIMATE statement will be used for the statistical test and to provide point estimate and confidence interval for the difference Treatment – Control.

The other secondary effectiveness endpoints will be analyzed by descriptive statistics including confidence intervals (CIs). For the iGAIS and sGAIS assessments, the proportion of subjects in the Treatment Group with any improvement [redacted] will be calculated and given as number of subjects with improvement/number of subjects in the corresponding analysis (n/N) and as percentage (%).

For the FACE-Q satisfaction with lower face and jawline, Rasch-transformed scores, ranging from 0 to 100, will be summarized for the Treatment Group using descriptive statistics. Higher scores reflect a better outcome. If missing data are less than 50% of the scale's items, the mean of the completed items will be inserted. [redacted]

13.4.2 Safety Analyses

All safety endpoints will be analyzed for the SES. Subjects will be analyzed as treated. Moreover, safety analyses will be based on the pooled randomized groups if not otherwise specified.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version that is in effect at the time the database is closed to allow for analysis by System Organ Class (SOC) and Preferred Term (PT).

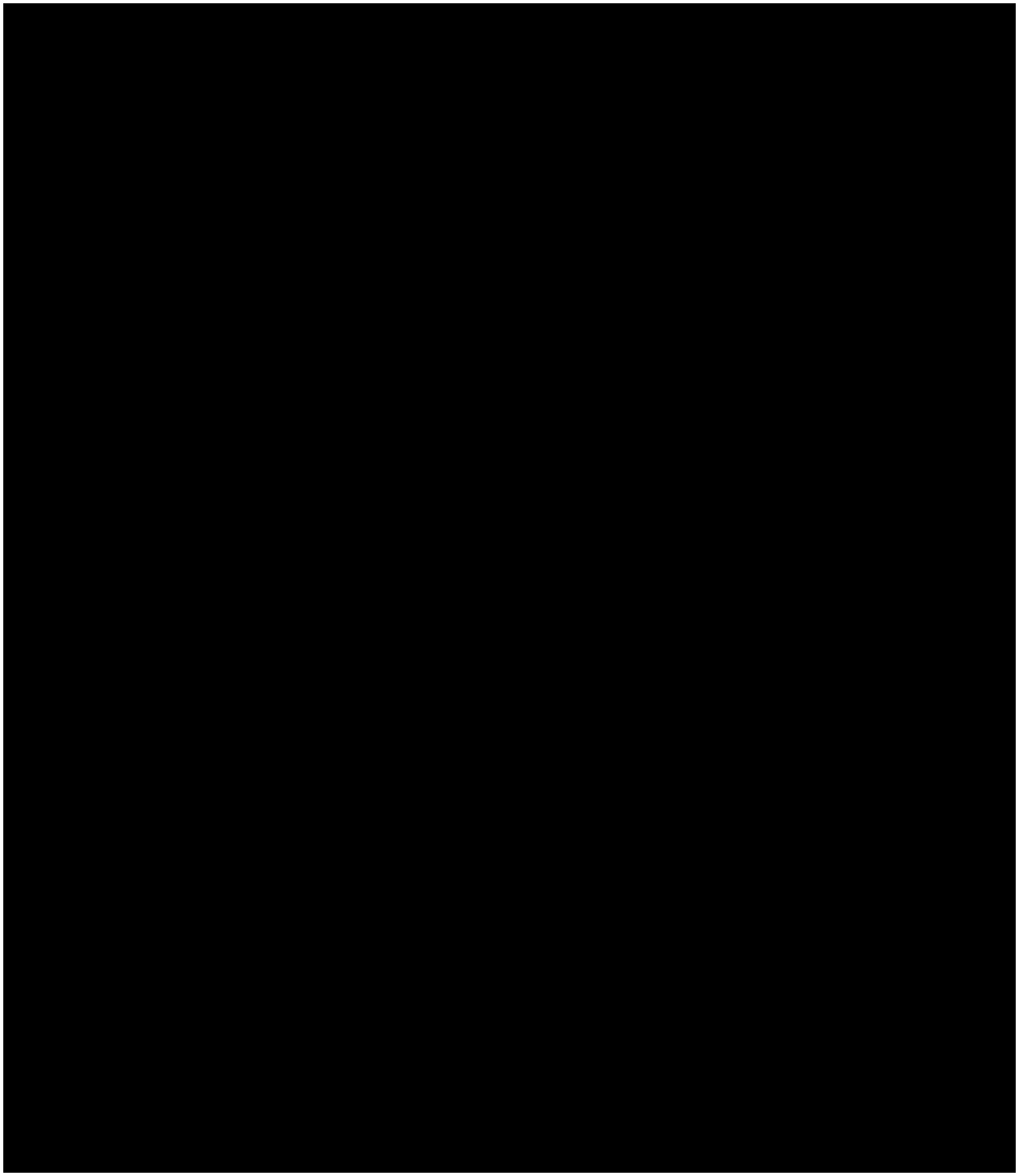
13.4.2.1 Secondary Safety Endpoints

The secondary safety endpoints are defined in Section 7.2.2.1.

Incidence rates of related TEAEs (Section 12.1.1) will be provided by PT:

- overall for all treated subjects;
- until Day 90 after treatment for all treated subjects;
- until Day 180 for the Treatment group.

[redacted]



13.5 Special Statistical/Analytical Issues

13.5.1 Subject Discontinuation and Missing Data

[redacted]

13.5.2 Interim Analyses

No interim analyses are intended.

13.5.3 Multiple Comparisons/Multiplicity

No multiplicity adjustments are intended.

[redacted]

14 ADMINISTRATIVE PROCEDURES

14.1 Trial Monitoring

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

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

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

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

14.2 Data Quality Assurance and Standardization Procedures

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

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

This trial will be monitored regularly by a qualified monitor from the CRO according to EN ISO 14155, Chinese GCP, Chinese regulatory authority requirements, and the respective standard operating procedures (SOPs; Section 14.1).

14.3 Source Documentation Requirements

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

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

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

14.3.1 Data Management

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

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

[redacted]

Further details will be described in the data management plan.

14.3.2 Data Review and Clarification Procedures

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

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

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

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

Entries from questionnaires (e.g., [redacted]FACE-Q; subject GAIS) completed by the subject will be entered into the eCRF by trial personnel. If corrections in the questionnaires are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date and initial the correction. The investigator should not make any changes to these documents. Per Chinese GCP, clinical trial records, as the original materials, must not be changed without authorization. If such a change is required, the reason shall be explained, and the explanation shall be signed and dated.

14.3.3 Direct Access to Source Data/Documents

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

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

14.3.4 Auditing

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

An audit can be conducted:

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 CTP deviations or suspicion of fraud;

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

e) when requested or suggested by a regulatory authority.

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

14.4 Protocol Deviations and Amendments

14.4.1 Protocol Deviations

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

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

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

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

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

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

14.4.2 Protocol Amendments

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

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

14.5 Record Retention

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

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

[redacted]

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

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

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

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

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

14.6 Clinical Trial Report

A clinical trial report containing effectiveness and safety analyses will be generated after all subjects have completed the Day 180 visit. The content of the report will meet China Center of Medical Device Evaluation (CMDE) requirements.

14.7 Publication of Trial Results

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

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

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

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

14.8 Financial Disclosure

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

14.9 Investigator Compliance

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

Additional information is reported in Section 14.4.1.

15 REFERENCE LIST

1. Chan NP, Shek SY, Yu CS, Ho SG, Yeung CK, Chan HH. Safety study of transcutaneous focused ultrasound for non-invasive skin tightening in Asians. Lasers Surg Med. 2011;43(5):366-75.

2. Fabi SG. Noninvasive skin tightening: focus on new ultrasound techniques. Clin Cosmet Investig Dermatol. 2015;8:47-52.

3. Mulholland RS. Radio frequency energy for non-invasive and minimally invasive skin tightening. Clin Plast Surg. 2011;38(3):437-48, vi.

4. Fitzpatrick RE. CO2 laser resurfacing. Dermatol Clin. 2001;19(3):443-51, viii.

5. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing. An evaluation of 500 patients. Dermatol Surg. 1998;24(3):315-20.

6. Ablon G. Safety and Effectiveness of an Automated Microneedling Device in Improving the Signs of Aging Skin. J Clin Aesthet Dermatol. 2018;11(8):29-34.

7. Sadick N. Tissue tightening technologies: fact or fiction. Aesthet Surg J. 2008;28(2):180-8.

8. Oni G, Hoxworth R, Teotia S, Brown S, Kenkel JM. Evaluation of a microfocused ultrasound system for improving skin laxity and tightening in the lower face. Aesthet Surg J. 2014;34(7):1099-110.

9. Hitchcock TM, Dobke MK. Review of the safety profile for microfocused ultrasound with visualization. J Cosmet Dermatol. 2014;13(4):329-35.

10. Dobke MK, Hitchcock T, Misell L, Sasaki GH. Tissue restructuring by energy-based surgical tools. Clin Plast Surg. 2012;39(4):399-408.

11. Valizadeh N, Jalaly NY, Zarghampour M, Barikbin B, Haghighatkhah HR. Evaluation of safety and efficacy of 980-nm diode laser-assisted lipolysis versus traditional liposuction for submental rejuvenation: A randomized clinical trial. J Cosmet Laser Ther. 2016;18(1):41-5.

12. Coleman S. Structural fat grafting: Thieme Medical Publishers, Incorporated; 2004.

13. Fabi SG, Joseph J, Sevi J, Green JB, Peterson JD. Optimizing Patient Outcomes by Customizing Treatment With Microfocused Ultrasound With Visualization: Gold Standard Consensus Guidelines from an Expert Panel. J Drugs Dermatol. 2019;18(5):426-32.

14. Klassen AF, Cano SJ, Scott A, Snell L, Pusic AL. Measuring patient-reported outcomes in facial aesthetic patients: development of the FACE-Q. Facial Plast Surg. 2010;26(4):303-9.

15. Pusic AL, Klassen AF, Scott AM, Cano SJ. Development and psychometric evaluation of the FACE-Q satisfaction with appearance scale: a new patient-reported outcome instrument for facial aesthetics patients. Clin Plast Surg. 2013;40(2):249-60.

16. Klassen AF, Cano SJ, Scott AM, Pusic AL. Measuring outcomes that matter to face-lift patients: development and validation of FACE-Q appearance appraisal scales and

adverse effects checklist for the lower face and neck. Plast Reconstr Surg. 2014;133(1):21-30.

17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis care & research. 2011;63 Suppl 11:S240-52.

16 APPENDICES