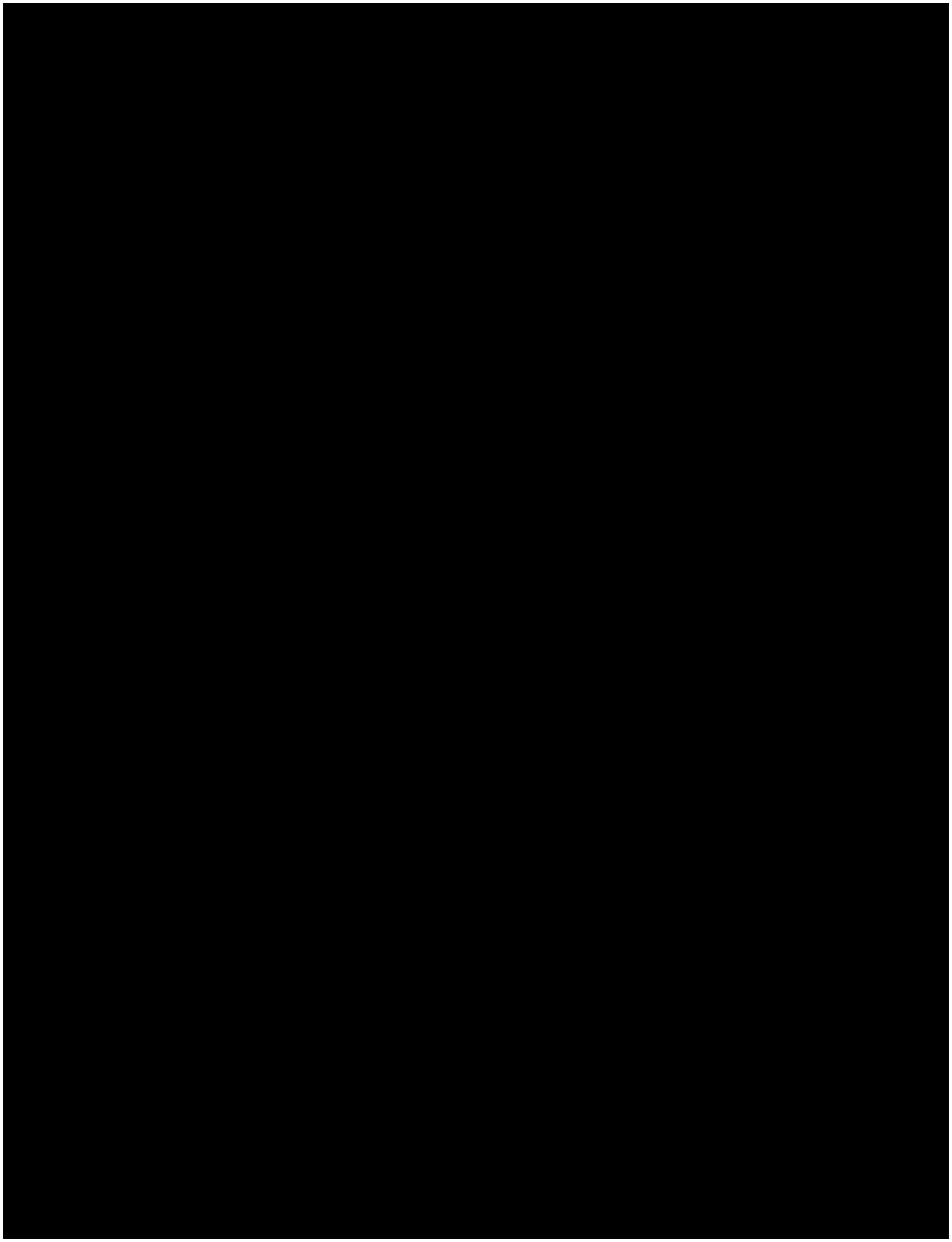
1 TITLE PAGE

Prospective, evaluator-blind, multicenter study to assess the safety and effectiveness of treatment with the Octave System for improving lines and wrinkles of the décolleté

Study Identifier:	M960101003 / NCT04681352
Version Date:	22-JUL-2021 (version 5.0; Amendment 4) 01-FEB-2021 (version 4.0; Amendment 3) 04-DEC-2020 (version 3.0; Amendment 2) 18-NOV-2020 (version 2.0; Amendment 1) 29-SEPT-2020 (version 1.0)
Investigational Medical Device:	Octave System
Indication:	Improvement in lines and wrinkles of the décolleté
Study Design:	Prospective, multicenter, evaluator-blind, staged, 180-day confirmatory study
Sponsor:	Ulthera, Inc., a division of Merz North America, Inc. / Merz Aesthetics

[redacted]

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



2 SYNOPSIS

Title of Study	Prospective, evaluator-blind, multicenter study to assess the safety and effectiveness of treatment with the Octave System for improving lines and wrinkles of the décolleté
Study Identifier	M960101003
Number of Sites and Countries	This study will be conducted at up to 10 investigational sites in the United States.
Investigational Medical Device	Octave System
Indication	Improvement in lines and wrinkles of the décolleté
Objective	To demonstrate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté.
Effectiveness Evaluation	*Primary endpoint* • Proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 90 (post-treatment) with baseline (pre-treatment) photographs. o Improvement is concluded if at least two of three independent, blinded evaluators assess the Day 90 standardized, photographic images as improved compared to baseline photographic images. *Secondary endpoint* • Proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 180 (post-treatment) with baseline (pre-treatment) photographs.
Safety Evaluation	*Secondary endpoint* • Incidence of treatment-emergent adverse events (TEAEs), related to Octave-Ultherapy treatment, as reported throughout the study.
Study Design Overview and Methodology	This is a 180-day, prospective, evaluator-blind, multicenter, staged, confirmatory study designed to evaluate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté. All enrolled healthy, adult female subjects with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté will receive a single Octave-Ultherapy treatment of the décolleté tissue with two transducers at energy level 4 [redacted] and one transducer at energy level 3 [redacted]. Subjects will be followed for 180 days, and photographs will be taken at baseline, Day 90, and Day 180. For the primary endpoint, improvement in the appearance of the décolleté will be determined by a blinded, independent assessment of photographs at 90 days post-treatment compared to baseline. The same photograph

	comparison will be made at 180 days post-treatment for the secondary endpoint. To reduce potential bias associated with evaluating only treated-subject photographs, images of untreated individuals, collected at two time points, will also be included for blinded, independent photographic review. Study subjects will have approximately 4 in-office study visits, including screening, baseline/treatment, a Day 90 (± 7 days) post-treatment visit, and a Day 180 (± 14 days) post-treatment visit. Follow-up telephone calls will occur at 3 days (± 1 day), 14 days (± 3 days), 28 days (+ 3 days), 120 days (± 7 days), and 150 days (± 7 days) after Octave-Ultherapy treatment. Expected study duration is approximately 8 months from screening of the first subject until final follow-up of the last subject. In Stage 1, an initial cohort of 10 subjects will be enrolled, safety data will be assessed up to Week 2, and subjects will participate until the Stage 1 study end at Day 90. In Stage 2, all enrolled subjects will participate until study end at Day 90 or Day 180 if reconsented for extended participation. The planned duration of participation for individual subjects is up to 30 weeks, including up to 21 days for screening, 1 day for treatment, and 90 or 180 days for follow-up.
Number of Study Subjects	Approximately 113 subjects are planned for screening to allow for 90 enrolled/treated subjects and 80 evaluable subjects in this study. In Stage 1, 10 subjects will be enrolled, while all other subjects will be enrolled in Stage 2.
Main Inclusion/ Exclusion Criteria	Key inclusion criteria are as follows: – Healthy female aged 35 to 65 years at the time of screening. – Moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention. [redacted] Key exclusion criteria are as follows: – Presence of an active systemic or local skin disease that may affect wound healing. – Scarring in area(s) to be treated. – Active implants (e.g., pacemakers or defibrillators), ports, or metallic implants in area(s) to be treated. – Breast implants or is planning to receive breast implants during the study. – Inability to take pre-treatment medications due to a pre-existing condition, medication allergy, or medical issue that, at the discretion of the treating investigator, is contraindicated.

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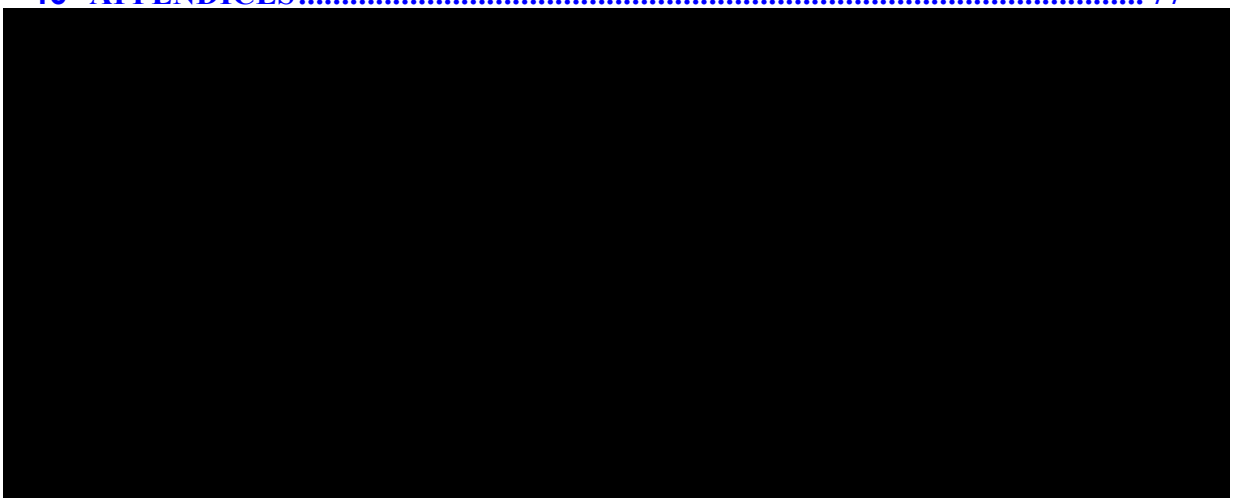

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
BL	Baseline
BMI	Body mass index
BRCA	BReast CAncer gene
CD	Compact disc
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSP	Clinical study protocol
[redacted]	
DS	DeepSEE
DVD	Digital versatile disc
eCRF	Electronic case report form
EDC	Electronic data capture
EL	Energy level
FCS LOGISTIC	Fully conditional specification logistic regression method
FDA	Food and Drug Administration (US)
FST	Fitzpatrick skin type
[redacted]	
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act of 1996 (US)
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Investigational device (term used interchangeably with investigational medical device (IMD))
IEC	Independent ethics committee
IFU	Instructions for use
[redacted]	

Abbreviation	Definition
IM	Intramuscular, as in treatment administration route
IMD	Investigational medical device (term used interchangeably with Investigational Device (ID))
IRB	Institutional Review Board
ISO	International Organization for Standardization (EN = English translation)
ITT	Intent to treat
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of non-missing observations
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OT	Octave System transducer
PHI	Protected health information
PO	Per os (Latin); used in medicine to describe treatment administration by oral route
PP	Per protocol
[redacted]	
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software®
Scr	Screening
SD	Standard deviation
[redacted]	
SOC	System organ class
SOP	Standard operating procedure
SP	Safety population
SPF	Sun protection factor
SSQ	Subject Satisfaction Questionnaire
TCP	Thermal coagulation point
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UADE	Unanticipated adverse device effect
US	United States
UV	Ultraviolet

5 ETHICS

5.1 Ethical Conduct of the Study

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

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

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

5.2 Informed Consent

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

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

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

During the study, the subject will be informed if information becomes available that may be relevant to the subject's willingness to continue participation in the study. Each ICF will include contact information (with a phone number) the subject should use to communicate any medical concerns 24 hours a day. The subject, however, is free to withdraw consent at any time and for any reason, whether expressed or not.

5.3 Subject Privacy

The subject will be informed of procedures to protect subject privacy. Under US federal law (the Privacy Rule), any protected health information (PHI) that is created or obtained during this study cannot be used or disclosed without permission. The currently designated statistical contract research organization (CRO) processes subject data in accordance with the data-protection provisions set forth in the German Federal Data Protection Act (Bundesdatenschutzgesetz), specifically in the version applicable as of 25-MAY-2018, and in the European-focused General Data Protection Regulation law (GDPR). Informed consent on data processing will be obtained in writing directly from the subject before recording of any data. Authorization to use and disclose PHI will be obtained in writing directly from the subject before recording of any data. Recorded data will be pseudonymized before transferring to authorized individuals. The investigator will maintain source documents linking unique subject numbers with subject names (e.g., in case of emergencies).

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

5.4 Confidentiality of Subject Information

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

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

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

6 INTRODUCTION

6.1 Background

Many factors contribute to the natural aging process during which an individual's skin gradually loses its youthful appearance. Aging skin is characterized by loss of volume, decreased elasticity, and increased laxity. Various aesthetic techniques have been used in an attempt to reverse or slow the aging process. As such, individuals are increasingly undergoing facial rejuvenation procedures; after treatment, they often notice the improved appearance of the face is in contrast with that of the untreated aging neck and chest. The chest and neck are exposed to substantial ultraviolet (UV) radiation and both regions tend to demonstrate photoaging. Additionally, the chest skin of females is vulnerable to the mechanical stress of the weight and movement of the breasts.[1] Aging of the skin in the décolleté region manifests as atrophy, laxity, wrinkles, and dyspigmentation.

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

Various energy-delivery devices, designed to create thermal injury to stimulate fibroblast synthesis and collagen production (e.g., fractionated ablative lasers, radiofrequency devices, fractional infrared devices), have been developed.[6] While these energy-based devices have demonstrated tightening effects on superficial layers of the skin, ultrasound energy can cause deeper skin-tightening effects by delivering focused energy to the dermis. Furthermore, ultrasound-energy use is associated with fewer adverse post-treatment effects when compared to epidermal treatments, due to its penetration of the deeper layers of skin while leaving the epidermal layers and intervening skin tissues unaffected.[7] This characteristic of microfocused ultrasound is particularly beneficial in patients of higher Fitzpatrick skin types (FST III to VI)[8], as melanocytes and melanin are superficial to the treatment location. As a result, microfocused ultrasound tends not to affect skin pigment and is safe for use in all FST.[9]

The Ulthera System is a non-invasive, dermatological, aesthetic treatment that is FDA cleared to lift the eyebrow (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. Ultherapy utilizes microfocused ultrasound energy with visualization (MFU-V) to create thermal coagulation points (TCPs)

in the deep reticular layer of the dermis and subdermis, while leaving the epidermal layers and overlying papillary dermis unaffected.[10] These thermal micro-injuries lead to collagen scaffold remodeling, which lifts the overlying skin and tightens the dermal layers.[10] Under the current clearance, DeepSEE® transducers are used in combination with the Ulthera System to incorporate high-resolution ultrasound imaging with ultrasound therapy. Using this ultrasonic visualization enables operator avoidance of ultrasound energy contact with large vessels and bone, as the technology can image to a tissue depth of 8 mm.

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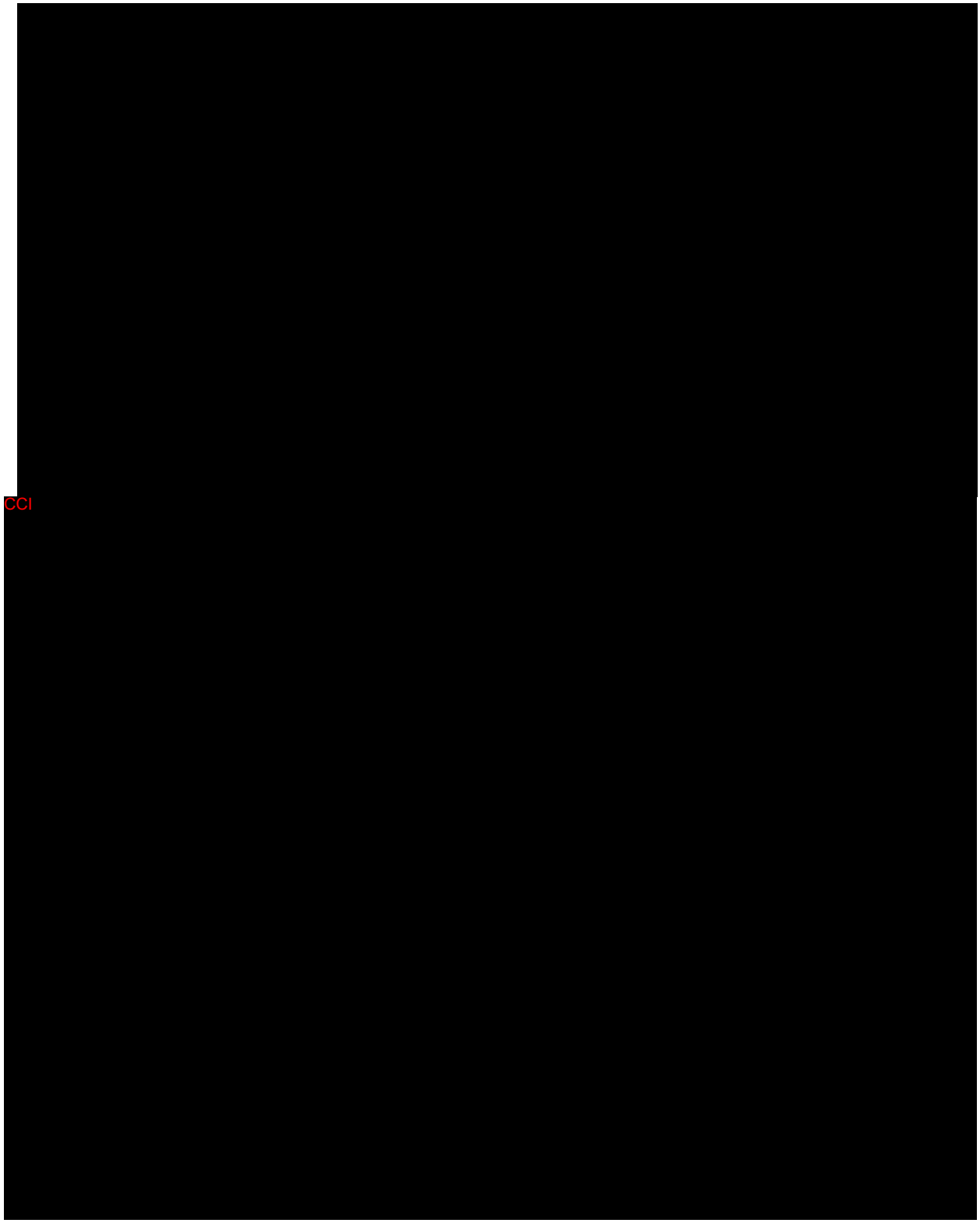
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6.2 Study Rationale

The current confirmatory study is designed to demonstrate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté. Analogous to the face and neck, changes in décolleté-skin tone and texture, including lines and wrinkles, occur with age, creating a concern for many individuals. Additionally, the chest skin of females is vulnerable to the mechanical stress of the weight and movement of the breasts, which can cause dynamic changes in the skin.[1] Ultherapy targets lines and wrinkles of the décolleté and offers a non-invasive approach to improving the aesthetic appearance of this region. Subjects with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention will be treated. Subjects will receive one Octave-Ultherapy treatment of the décolleté tissue and will be followed for 90 or 180 days. Previous studies have shown improvement in the aesthetic appearance of the décolleté region after DeepSEE Ultherapy treatment as early as 90-days post-treatment [redacted]; thus, subjects will be followed for the same length of time for the primary endpoint. Subjects will be treated with two

Octave System transducers at energy level 4 [redacted] and one Octave System transducer at energy level 3 [redacted] using a treatment map similar to those used in prior studies.

Although all FST are eligible for study enrollment, the current protocol proposes that approximately 90% of the total sample size will include subjects with an FST I, II, or III, and approximately 10% of subjects will be FST IV, V, or VI. As stated in Section 6.1, MFU-V can be used across the FST range as MFU-V does not affect the epidermis, melanocytes, or melanosomes and is blind to chromophores.[8, 9] In fact, the pigmentation effect of the Ulthera System was categorized as "chromophore insensitive" in the original 510(k) submission and subsequent clearance for eyebrow [redacted]. Due to delays in aging of the skin, moderate to severe laxity of the décolleté is not typically found in individuals of higher FST, even when increasing the age limit beyond 65 years (i.e., beyond our proposed intended use population).[11-14] Higher FSTs were also not treated in the clearance study of the predicate device, the Ulthera DeepSEE System [redacted]. Based on this scientific and practical rationale, we have planned to include at least 10% of higher FST (IV, V, VI) in our Octave décolleté study population. This approach reflects the population that is likely to seek this treatment for the décolleté.

6.3 Potential Benefits and Risks

The potential benefit of Ultherapy on the Octave System is improvement of lines and wrinkles of the décolleté. Additionally, the results of this study may contribute to further development of the ultrasound-based, non-invasive, tissue-tightening procedure.

Potential risks associated with the use of Ultherapy on the Octave System include localized acute and/or post-procedure pain or discomfort, erythema (redness), edema (swelling), wheals, tenderness to touch, bruising, and temporary nerve effects. Pre-treatment medications proposed for use in this study can cause nausea, lightheadedness, stomach upset, and constipation (Section 10.5.1.2). The rare 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, poor transducer to skin coupling, incorrect line spacing, gel pockets). Some scars may respond to medical treatment. Additionally, the following AEs have been identified during routine, post-market clinical use of 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; pruritus; blistering; scarring; discoloration; and hyperpigmentation. These AEs were chosen for inclusion in the Ulthera DeepSEE System Instructions for Use (IFU) due to a combination of their seriousness, frequency of reporting, or potential causal connection to the Ulthera DeepSEE System. However,

because these AEs are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship with the Ulthera DeepSEE System.

In clinical trials with the first-generation Ulthera DeepSEE system, no device- or procedure-related serious adverse events (SAEs) were observed, and reported adverse events (AEs) were generally expected, mild in nature, and short in duration.[7, 15-17] Long-term follow-up studies confirmed the favorable safety profile of the Ulthera DeepSEE system with primarily mild, treatment-related side effects.[10]

Risks of Ultherapy on the second-generation Octave System will be minimized or reduced by training the investigational sites and monitoring the subject during the treatment procedure, with careful observation of the subject's pain and skin response to treatment. Previous clinical studies with the Ulthera DeepSEE System have shown the sensory response was tolerable from both the subject's and investigator's perspective.[10] Discomfort was transient, and acute pain resolved within 30 minutes. If the subject is uncomfortable during Octave System treatment, the treating investigator has the option to utilize additional measures to improve tolerability, including additional/different pain medication (e.g., see Section 10.5.1.2). If treatment remains intolerable after implementation of mitigation measures, the investigator or delegated study clinician must stop administering treatment, for the subject's safety, and the subject will be followed for AEs throughout the study's duration. In the case of an AE report, the subject will be followed until the subject's last study visit, until the AE is resolved or stabilized, the subject is lost to follow-up, or some other resolution of the event occurs.

Considering all risks and benefits of Ultherapy on the Octave System, the potential benefits to physicians and subjects seeking treatment outweigh the potential risks. The benefit/risk ratio of the device is considered acceptable when used on subjects seeking improvement of lines and wrinkles of the décolleté.

Additional information on device- and procedure-related contraindications, warnings, and precautions can be found in the current version of the Octave System IFU CCI [redacted]

7 STUDY OBJECTIVE AND ENDPOINTS

7.1 Objective

The objective of this study is to demonstrate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté.

7.2 Endpoints

7.2.1 Effectiveness Endpoints

7.2.1.1 Primary Effectiveness Endpoint

- Proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 90 (post-treatment) with baseline (pre-treatment) photographs.
    - Improvement is concluded if at least two of three independent, blinded evaluators assess the Day 90 standardized, photographic images as improved compared to baseline photographic images.
    - The success criterion is defined by achieving simultaneously a point estimate ≥ 65% and a lower bound of the one-sided 95% Wilson confidence interval > 50% for the proportion of treated subjects with improvement.

7.2.1.2 Secondary Effectiveness Endpoint

- Proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 180 (post-treatment) with baseline (pre-treatment) photographs.

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[redacted]

7.2.2 Safety Endpoints

7.2.2.1 Secondary Safety Endpoint

- Incidence of treatment-emergent adverse events (TEAEs) related to Octave-Ultherapy treatment, as reported throughout the study.

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[redacted]

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8 CLINICAL INVESTIGATION PLAN

8.1 Overview of Study Design

This is a 180-day, prospective, evaluator-blind, multicenter, staged, confirmatory study designed to evaluate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté. Approximately 90 subjects will be enrolled at up to ten investigational sites in the United States. All FST will be eligible for study enrollment. It is estimated that approximately 90% of the total sample size will consist of subjects with FST I, II, or III, and approximately 10% of subjects will be FST IV, V, or VI. Subjects enrolled will be healthy females, aged 35 to 65 years at the time of screening, with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention. Prior to study start, all investigators will be trained on appropriate enrollment criteria, focused on moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté, using photo booklets. Additionally, for each site, approximately the first four to five subjects with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté, as selected by the investigator for potential enrollment, will be confirmed for study-appropriate lines and wrinkles of the décolleté via an independent photographic reviewer.

In this non-comparative, staged, confirmatory study, investigators and subjects will not be blinded to treatment, subjects will not be randomized, and all enrolled subjects will receive a single Octave-Ultherapy treatment of the décolleté tissue with two transducers at energy level 4 [redacted] and one transducer at energy level 3 [redacted]. In Stage 1, an initial cohort of subjects will be enrolled, safety data will be assessed up to Week 2, and subjects will participate until Stage 1 study end at Day 90. In Stage 2, all enrolled subjects will be followed for 90 days or 180 days if reconsented for extended participation. In addition, to reduce potential bias associated with using only treated-subject photographs for evaluation, photographs of approximately 30 untreated individuals, who meet selected appearance criteria (Section 11.2.1.1.1), will be collected at two different time points and subsequently paired for evaluation by the independent, blinded evaluators. Using this 3:1 ratio of treated subjects to untreated individuals, image sets of these untreated individuals will be randomly distributed among the pre- and post-treatment image sets of the treated subjects and presented to the blinded evaluators. For the primary effectiveness endpoint, the "baseline" photograph will be identified as "Photograph 1", and the independent evaluators will be blinded to the randomly distributed treated versus untreated status of the comparator Photograph 2 (i.e., Day 90 post-treatment among treated subjects or post-baseline for untreated individuals). The same photographic assessment will be used for the secondary effectiveness endpoint with the comparator Photograph 2 collected at Day 180 post-treatment. Additional information on the methodological plan, detailing photograph collection through subsequent presentation to

blinded evaluators, will be provided in a supporting document, developed collaboratively between the sponsor and the photography vendor.

Study subjects will have approximately 4 in-office study visits, including screening, baseline/treatment, a Day 90 (± 7 days) post-treatment visit, and a Day 180 (± 14 days) post-treatment visit. Follow-up telephone calls will occur at 3 days (± 1 day), 14 days (± 3 days), 28 days (+ 3 days), 120 days (± 7 days), and 150 days (± 7 days) after Octave-Ultherapy treatment. The primary effectiveness endpoint, the proportion of treated subjects with improvement in lines and wrinkles of the décolleté, will be evaluated using a blinded, independent assessment of photographs at post-treatment Day 90 compared to baseline. Improvement is concluded if at least two of three independent, blinded evaluators assess the Day 90 standardized, photographic images as improved compared to baseline photographic images.

Standard safety evaluations, including the incidence of AEs and SAEs, will be assessed.

[redacted]

Section 11.1 [redacted] detail a full schedule of study events and a schedule of events for each visit.

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

As detailed in Section 8.1, this is a 180-day, prospective, evaluator-blind, multicenter, staged, confirmatory study designed to evaluate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté.

The 90-day minimum study duration represents a reasonable timeframe to assess effectiveness, as well as longer-term safety.[10, 18, 19] The multicenter design approach will increase the representativeness of study results and decrease site-related biases. Treatment guidelines in the current protocol (Section 10.5.1.3) follow those used for clearance of improved lines and wrinkles of the décolleté on the Ulthera DeepSEE System [redacted].

Lastly, all enrolled subjects will receive treatment, and no control group is planned. However, following guidance provided by the FDA and to reduce potential bias associated with using only treated subjects' photos for evaluation, paired photographs of approximately 30 untreated individuals, collected at two time points by the central photography vendor (Section 11.2.1.1.1), will be randomly distributed among the pre- and post-treatment paired photos of treated subjects, and all will be presented to the blinded, independent photographic evaluators (Section 11.2.1.1).

9 STUDY POPULATION AND RESTRICTIONS

9.1 Number of Subjects and Sites

Approximately 80 evaluable subjects, who complete the full Ultherapy treatment session using the Octave System, are planned for this study. Assuming a screen failure rate of 20%, approximately 113 subjects will be screened; assuming attrition of 10 subjects, approximately 90 subjects are planned for enrollment/treatment. All subjects will sign and date the ICF before any study-related procedures are undertaken.

In Stage 1, 10 subjects will be enrolled at a minimum of two investigational sites (maximum: 6 sites) in the United States, while all other subjects will be enrolled in Stage 2. Number of investigational sites will not exceed ten in total. During Stage 1, Week 2 safety data for the first 10 treated subjects will be evaluated. All 10 subjects enrolled in Stage 1 will participate until Stage 1 study end at Day 90. In Stage 2, all other enrolled subjects will participate for at least 90 days (± 7 days), with a maximum duration of 180 days (± 14 days) if reconsented for extended participation. Females of all FST are eligible for study participation. In addition, approximately 10% of the enrolled subjects will be categorized as FST IV, V, or VI, and of which 5% will be categorized as FST V or VI.

Subjects who are enrolled and who do not complete the study will not be replaced. Furthermore, the secondary effectiveness endpoin [redacted] at Day 180 will only be assessed among subjects who reconsent at their Day 90 visit for extended study participation to Day 180.

Photographs of approximately 30 untreated individuals, who meet selected appearance criteria (Section 11.2.1.1.1), will be collected at two different time points, between 1 day and 1 week apart; these photographs will be subsequently paired for evaluation by the independent, blinded evaluators.

To confirm the presence of appropriate anatomy at the intended depth of treatment (see Inclusion Criterion #3 in Section 9.2.1), the treating investigator will use the Octave System's supplemental imaging mode to visualize the dermal and subdermal layers of tissue. For example, subjects with bone, rather than soft tissue, at the intended treatment depth would be considered screen failures and would not be eligible for enrollment.[16]

Additional information regarding subject enrollment is provided within the sample size justification (Section 13.1).

9.2 Selection of Subject Population

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

9.2.1 Inclusion Criteria

To be eligible for study participation, the treating investigator will ensure each subject meets all study inclusion criteria at the screening (Scr) and/or baseline (BL) visit as follows:

Inclusion criteria	Scr	BL
1. Healthy female aged 35 to 65 years at the time of screening.	X	
2. Moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention.	X	
[redacted]	[redacted]	
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9.2.2 Exclusion Criteria

Subjects meeting any of the following criteria at the screening (Scr) and/or baseline (BL) visit are not eligible to participate in the study:

Exclusion criteria	Scr	BL
[redacted] Presence of an active systemic or local skin disease that may affect wound healing.	X	X
[redacted] Scarring in area(s) to be treated.	X	X
CCI [redacted]	CCI	[redacted]
[redacted] Active implants (e.g., pacemakers or defibrillators), ports, or metallic implants in area(s) to be treated.	X	X
[redacted] Breast implants or is planning to receive breast implants during the study.	X	X
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Exclusion criteria	Scr	BL
CCI		
Inability to take pre-treatment medications due to a pre-existing condition, medication allergy, or medical issue that, at the discretion of the treating investigator, is contraindicated.	X	X
CCI		

Exclusion criteria	Scr	BL
CCI [redacted]		

[redacted]

CCI [redacted]

9.2.4 Subject Enrollment

Subjects are considered to be enrolled when they provide informed consent (i.e., sign the ICF), meet all eligibility criteria, or are treated.

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 treated at the baseline visit 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. In cases when a subject is not meeting eligibility criteria due

to a temporary condition, this subject may be rescreened, at the discretion of the treating investigator, upon resolution of the temporary condition.

9.2.6 Removal of Subjects from Therapy or Assessment

9.2.6.1 Treatment Discontinuation

If study treatment is discontinued during administration, the investigator will record the reason for treatment discontinuation in the study records. Potential reasons for discontinuation of treatment may include refusal by the subject to receive additional treatment or physician's decision. The investigator should request that a subject discontinuing treatment continue to participate in the study and complete all remaining visits and safety follow-up assessments. For subjects declining continued study participation after treatment discontinuation, additional information regarding subject withdrawal is provided in Section 9.2.6.2.

If the subject experiences escalating pain during the Ultherapy procedure that is not adequately controlled with the initially selected treatment regimen, the investigators may use their discretion to utilize further protocol-specific options to control pain (Section 10.5.1.2). Attempts should be made to optimize pain medication so that treatment can be completed.

9.2.6.2 Subject Withdrawal or Discontinuation

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

Subjects have the right to withdraw from the study at any time at their own request without prejudice. In cases of withdrawn consent, data collected until the date consent was withdrawn will be analyzed as recorded.

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

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

The reason for the subject's discontinuation should be documented in the electronic case report form (eCRF). The investigator should make every attempt to complete the recommended follow-up assessments specified for the End of Study/Early Termination visit specified in the Schedule of Events (Section 11.1 [redacted]), while fully respecting the subject's rights.

In the case of a reported nerve effect leading to paresthesia or weakness, as well as any severe unanticipated AE that is determined to be an AE related to the device treatment, a root-cause investigation will be conducted to determine the cause, the outcome of the event, and status of subject. The investigator and the sponsor will conduct a thorough evaluation of the event. The sponsor will then immediately make a determination if the study should be suspended (Section 9.2.8).

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

9.2.6.3 Provision of Care for Subjects after Study Discontinuation

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

9.2.7 Suspension or Premature Termination of a Study Site

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

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

The sponsor will provide the investigational 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 investigational 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 investigational site resumes trial activities. If subjects were informed of the suspension, the principal investigator or authorized designee will inform them of the reasons for resumption.

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

In the event of a pandemic disease outbreak (e.g., new COVID-19 public health emergency), it may not be feasible for an investigational site to continue study participation. In this scenario, consideration will be given to the impact of investigative-site closure on the safety and well-being of participating subjects.

9.2.8 Suspension or Premature Termination of the Study

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

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

- Determination of a potential safety risk to subjects;
- Inadequate subject enrollment;
- Decision by the IEC/IRB to suspend or terminate approval/favorable opinion for the study; and/or
- Sponsor decision.

If suspicion of an unacceptable risk to subjects arises during the trial or if instructed by the IEC/IRB or regulatory authorities, the sponsor will 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.

In the event of study suspension or premature termination, the sponsor will inform all investigators and relevant regulatory authorities promptly of the study suspension/ termination and reason for the action, as detailed in Section 9.2.7. The investigator will conduct site-closure activities in accordance with all applicable sponsor, local, and international guidelines and regulations.

9.2.9 Subject Completion

Subjects are considered to have completed the study if they receive full treatment and complete all visits defined in the Schedule of Events (Section 11.1[redacted]).

9.2.10 End of Study

The end of the study is defined as when the last subject completes the last visit and the database is closed.

10 STUDY DEVICE AND TREATMENT OF SUBJECTS

10.1 Description of Study Device

The Octave System is the second-generation Ulthera platform technology. The new Octave System is to be marketed for the same intended use and indications for use as the cleared DeepSEE system (Ulthera System K180623; originally launched in the US in 2009), namely for non-invasive dermatological aesthetic treatment to improve lines and wrinkles of the décolleté.

[redacted]

[redacted] The Octave System consists of four primary components (console, handpiece, transducers, and cart) that allow the user to visualize and precisely deliver therapeutic heat to select tissue layers within the skin using microfocused ultrasound.

CCI [redacted]

A variety of transducer designs is available at different frequencies and nominal treatment depths [redacted].

[redacted]

CCI [redacted]

Reference the current IFU CCI [redacted] for additional information related to the Octave System's technological characteristics.

10.1.1 Mechanism of Action

[redacted]

10.1.2 Operating Information

[redacted] the user interface displayed during treatment is dominated in the center by the ultrasound image. Other control and information panels surrounding the ultrasound image enable changes in the energy level, monitor line delivery, track the treatment depth, and allow the activation of imaging and storing of ultrasound images. [redacted]

When a treatment zone is selected using therapy controls on the touch panel, the energy, spacing, and length parameters will be preset to study-specific values. The maximum number of TCPs and spacing are fixed and dependent on the specific transducer inserted into the handpiece. For this clinical trial, the treating investigator will not be able to adjust the energy level – that is, all study subjects must be treated with two transducers at energy level 4 [redacted] and one transducer at energy level 3 [redacted], with **no reduction in energy level permitted** according to the study protocol. [redacted]

CCI [redacted]

CCI

[redacted]

10.2 Instructions for Use and Administration

The investigational device should be used in the décolleté region in accordance with the information presented in Section 10.3. Additional information on product usage is provided in the current version of the Octave System IFU CCI [redacted]

It is recommended that the following areas be avoided during treatment with the Octave System:

- Thyroid gland, thyroid cartilage, and trachea;
- Major vessels;
- Breast tissue.

The Octave System should only be used by those trained and qualified to operate. For this clinical trial, such training will be provided by the sponsor before the start of the study. Additionally, should study personnel change during the trial, the sponsor will retrain, as necessary.

10.3 Methods of Assigning Subjects to Treatment Groups

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

Each subject will receive a unique subject number upon entry in the EDC system. In cases when subjects are not eligible for enrollment at the baseline visit (e.g., due to a temporary condition), they will be considered a screen failure. Rescreening of such a subject is allowed upon resolution of the temporary condition. In this case, a new screening number will be assigned, and all screening assessments will be repeated.

All subjects will receive a single Ultherapy treatment on the Octave System – that is, no randomization will be used.

10.4 Blinding Procedures

In this non-comparative study, investigators and subjects will not be blinded to treatment. Three independent, photographic evaluators will be blinded for the primary effectiveness endpoint as described in Section 8.1.

10.5 Study Treatment

All protocol-specific criteria for the administration of study treatment must be met and documented prior to the start of any study treatment. All treatments with the investigational device will be performed on site by the treating investigator or by delegated and qualified study personnel. Subjects will not be dispensed any investigational material. Any noncompliant subject or site may be discontinued from the study (Section 9.2.6.2 and Section 9.2.7, respectively).

10.5.1 Planned Treatment Procedure and Administration

Subjects will be enrolled to receive treatment of the décolleté with two transducers at energy level 4 [redacted] and one transducer at energy level 3 [redacted]. **No reduction in energy level is permitted** under this study protocol.

10.5.1.1 Pre-Treatment Assessments

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

10.5.1.2 Pre-Treatment Medications and Procedure

[redacted]

[redacted]

10.5.1.3 Treatment Region and Administration Procedure

The general anatomic boundaries of the décolleté treatment region are delineated superiorly by the sternoclavicular notch, laterally by the midclavicular line, and inferiorly by the superior point of the intermammary cleft. Although variations in the anatomy of medial breast tissue may occur, all investigators will be trained to avoid treating in an area overlying or including breast tissue.

[redacted]

To ensure appropriate collection of pain data [redacted], each region should receive the full line count with each transducer [redacted] before moving to the next region.

Laterality is the subject's right or left.

For this clinical trial, the treating investigator will not be allowed to adjust the energy level – that is, all study subjects must be treated at the pre-defined energy level [redacted], with **no reduction in energy level permitted** according to the study protocol. Additionally, study subjects administered line counts that differ by ± 10% of the treatment guideline will be categorized as receiving a full treatment and will not be considered protocol deviations [redacted].

Investigators will be trained by the sponsor to use Octave System ultrasound imaging to ensure proper treatment is delivered (e.g., contact, depth).

CCI [redacted]

CCI

[redacted]

CCI

10.5.2 Selection and Timing of Treatment for Each Subject

At the baseline visit, all enrolled healthy, adult subjects with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté will receive a single Octave-Ultherapy treatment of the décolleté tissue according to the treatment guidelines presented in Section 10.5.1.3. No additional treatments will be offered under this study protocol.

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 **Imaging/Ready** button on the handpiece or console to discontinue treatment in progress, and/or press the red emergency **Stop** button to completely halt console operation.

As described in Section 10.5.1.2, should the subject experience escalating pain during the Ultherapy procedure that is not adequately controlled with the previously selected treatment regimen, the investigators may use their discretion to utilize further protocol-specific options to control pain. If the pain experienced by the subject remains intolerable after having administered the maximum allowable limit and type of treatment medications, treatment should be discontinued, and the subject will be followed for safety only.

10.6 Prior and Concomitant Therapy

Medical history and concomitant therapies, including pre- and post-treatment pain measures, that are deemed relevant for study conduct by the investigator (e.g., chronic

diseases, previous aesthetic treatments) should be documented in the eCRF. [redacted]

10.7 Study Supplies and Packaging of Treatment Supplies

Sites will be supplied with the Ulthera Octave System, including console, handpiece, transducers, and cart. This investigational medical device (IMD) is to be used exclusively for treatment of subjects enrolled in this study and will be labeled as follows: "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use." Device labels will also note the manufacturer name and address and the quantity within the package. An IFU [redacted] will be provided with each system.

Sites will also be supplied with study-specific ultrasound gel, cleanser for washing of the treatment area, and a handheld mirror.

10.8 Receipt, Storage, Dispensing, and Return/Disposal

Upon receipt, study personnel will verify the contents of all study supplies received and promptly notify the sponsor of any discrepancies or damages. The investigator or designee will keep a record of the study-product delivery to the study site.

All study devices must be stored in a secure area.

Only authorized study personnel may administer pain medication and study treatment, and only subjects enrolled in the study may receive the investigational treatment. The investigator is responsible for maintaining a current, accurate record of all study-treatment dispensation.

At the end of the study and after verification of study-equipment accountability, it is the investigator's responsibility to return all unused and used IMD equipment (i.e., console, handpiece, transducers, and cart) to the sponsor. Appropriate records of return must be maintained for accountability purposes.

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

10.9 Device Accountability Procedures

All necessary study supplies will be released to the investigator after approvals of the study protocol have been received by the sponsor from the IEC/IRB. Accountability for study supplies at the investigational site is the responsibility of the investigator. Access to the IMD will be controlled, and the IMD will be used only in the clinical investigation and

according to the clinical study protocol. The sponsor will keep records to document the physical location of all IMDs from shipment to the investigational sites until return or disposal. The investigator or an authorized designee is responsible for ensuring that accurate records of receipt, use, return, and disposal of the IMD, are maintained and include:

- Date of receipt.
- Identification of each IMD (batch number/serial number or unique code).
- Expiration date.
- Date or dates of use.
- Unique subject number.
- Date of return of unused, expired, or malfunctioning IMD (if applicable).

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

Lastly, dispensing records of treatment lines are recorded on the subject's treatment record, which is automatically generated by the Ulthera System. These data will be entered to the EDC system. An overall accountability log will be maintained, documenting the number of treatment lines per subject.

10.10 Treatment Compliance

The single treatment session will be administered by the treating investigator or by delegated and qualified study personnel. Variations from the defined study-treatment administration will be reported as protocol deviations. See Section 10.5.1.3 for additional details.

10.11 Duration of Study

Subjects are screened at the screening visit and enrolled and treated at the baseline visit. Expected study duration is approximately 8 months from screening of the first subject until final follow-up of the last subject. In Stage 1, an initial cohort of subjects will be enrolled, safety data will be assessed up to Week 2, and subjects will participate until Stage 1 study end at Day 90. In Stage 2, all enrolled subjects will participate for at least 90 days (± 7 days), with a maximum duration of 180 days (± 14 days) if reconsented for extended participation. The planned duration of participation for individual subjects is up to 30 weeks, including up to 21 days for screening, 1 day for treatment, and 90 (± 7) days or 180 (± 14) days for follow-up.

11 STUDY PROCEDURES

11.1 Visit Schedule

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

The purpose of the screening visit (Visit 1) is to determine subject eligibility for study participation and must be completed no more than 21 days prior to Day 1 (Visit 2). Informed consent is to be obtained at the screening visit, and the reviewing/recording of AEs begins upon ICF signature. Subject demographics, including FST [redacted], should be recorded in the eCRF, and a subject-reported medical history is acceptable.

> *Note: Additionally, for each site, approximately the first four to five subjects with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté, as enrolled by the investigator, will be confirmed for study-appropriate lines and wrinkles of the décolleté via an independent photographic reviewer.*

In addition to the activities listed in the Schedule of Events [redacted],

- At Visit 2 (Day 1), prior to performing the investigator's skin examination, the subject must wash the treatment area to remove any moisturizers/emollients, makeup, bronzing agents, etc. on the neck/décolleté region, if necessary.
- [redacted] study personnel should schedule follow-up phone call(s) and Visit 3.
- At Visit 3, subjects will be requested to reconsent for extended study participation to 180 days. If reconsented, study personnel should schedule follow-up Day 120 and Day 150 phone call(s) and Visit 4.
- All required subject-related, pre-treatment procedures and assessments should be completed before the administration of oral or IM pain medication (Section 10.5.1.2).
- After administration of the pain medication, study personnel should verify all study-specific treatment settings on the Octave System and prepare study-specific materials needed for treatment (e.g., ultrasound gel). Study personnel should prepare inhaled nitrous oxide/oxygen mixture for potential use, if available.

All subjects will receive a single, site-administered Ultherapy treatment using the Octave System (Section 10.5.1.3) on Day 1 (Visit 2). Subject-reported pain associated with treatment will be assessed after completing treatment with each transducer and for each region treated (Section 11.2.2.2.3). Importantly, if the subject experiences escalating pain during the Ultherapy procedure that is not adequately controlled with the initially selected treatment regimen, the investigators may use their discretion to utilize further protocol-specific options to control pain (Section 10.5.1.2). Due to pre-treatment and intra-

procedural medications, subjects must have a driver following the study treatment visit (Section 10.5.1.2).

Subjects will be contacted by telephone 3, 14, 28, 120, and 150 days after treatment and will be required to present for an unscheduled visit if indicated by safety concerns. [redacted] Safety follow-up will occur until Day 90 ± 7 days or Day 180 ± 14 days for subjects who reconsent for extended participation.

The primary endpoint visit will occur at Visit 3 (Day 90 ± 7 days). Prior to performing the investigator's skin examination, the subject must wash the treatment area to remove any moisturizers/emollients, makeup, bronzing agents, etc. on the neck/décolleté region, if necessary. [redacted]

Importantly, in the case of premature discontinuation of the study, a final assessment (End of Study visit) should be performed.

11.1.1 Scheduled Visits

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

11.1.2 Unscheduled Visits

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

[redacted]

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

11.2 Study Assessments and Definitions

11.2.1 Effectiveness Assessments

The effectiveness of the Octave System to improve lines and wrinkles of the décolleté will be evaluated using several methods, including qualitative assessment of photographs by three blinded evaluators.

Refer to the respective endpoints (Section 7.2) and visit schedules (Section 11.1 [redacted]) for additional information on the effectiveness assessments.

11.2.1.1 Standardized 2D Photographs

For assessment of the primary effectiveness endpoint, standardized 2D photographs will be taken at the screening visit and at Day 90, at a minimum. Among reconsented subjects, additional standardized 2D photographs will be taken at Day 180. A frontal view of the décolleté is to be obtained using the camera system provided, paired with the Canfield IntelliStudio platform to standardize image capture. Standardized 2D photographs will be utilized to complete the independent photographic review [redacted]

Since photographs are of critical importance as a reference measure throughout the study, the 2D photographs taken at the screening visit (Visit 1) will be reviewed and accepted by the central photography vendor prior to treatment. If a subject's screening photographs are deemed unsatisfactory by the central photography vendor, photographs will be retaken at Visit 2. Any additional photographs collected at Visit 2 must be collected prior to treatment administration. If no repeat photography is needed, the screening photographs will default to the baseline (pre-treatment) photographs and will be used for reference throughout the study.

At each site, the respective study photographers must be trained in taking standardized photographs and follow the instructions provided in a separate photography user manual. It is of the utmost importance that subjects are photographed in highly standardized positions and with the same setup (i.e., standardized distance, area, views, color standard, lighting, and background). Every effort should be made to have the same trained study personnel take photographs at every visit, and to maintain the setup of the photo studio over the course of the study, with the identical and exact fixed camera positions for the different views and light setups.

11.2.1.1.1 Photographs of Untreated Individuals

Photographs of approximately 30 untreated individuals will also be prepared, providing a subset of untreated photographs for assessment by the blinded evaluators.

After removing any moisturizers/emollients, makeup, bronzing agents, etc. on the neck/décolleté region, these untreated individuals will be required to meet selected appearance criteria as follows:

- Female aged 35 to 65 years.
- Moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention.
- No scarring in the décolleté region.
- No tattoos in the décolleté region.
- No open wounds or lesions in the décolleté region.
- No active, cystic, or severe inflammatory acne in the décolleté region.
- No evidence of recent excessive or prolonged exposure to sunlight, tanning booths, sun lamps, or UV-light sources in the décolleté region.
- No evidence of recent use of pigmenting agents (e.g., self-tanning agents, bleaching/depigmenting agents) in the décolleté region.
- No evidence of recent medical procedures in the neck, breast, shoulder, arm, or chest region.
- Willingness to avoid excessive or prolonged exposure to sunlight, tanning booths, sun lamps, or UV-light sources until second photo is taken.
- Willingness to avoid the use of pigmenting agents (e.g., self-tanning agents, bleaching/depigmenting agents) until second photo is taken.
- Willingness to avoid any elective neck, breast, shoulder, arm, or chest surgery, procedure, or treatment until after the second photo is taken.

Untreated individuals will be screened and selected by a third-party vendor, responsible for conducting all photography services. Eligibility of untreated individuals will be based on study-specific appearance only, as listed above, and will be confirmed by the sponsor's medical expert. Photographs of untreated individuals will be taken at two different time points, between 1 day and 1 week apart.

Additional information on the methodological plan, detailing photograph collection through subsequent presentation to blinded evaluators, will be provided in a supporting document, developed collaboratively between the sponsor and the photography vendor.

Results of the independent photographic review for the untreated individuals will be recorded.

11.2.1.1.2 Photographs for Independent, Blinded Evaluation

To assess the proportion of treated subjects with improvement in lines and wrinkles of the décolleté from baseline to Day 90 (i.e., primary effectiveness endpoint) and to Day 180 (i.e., secondary effectiveness endpoint), three independent, blinded evaluators will assess paired, 2D photograph sets of treated subjects and untreated individuals, according to the procedure described below. These evaluators will be experienced, non-treating physicians, who are board-certified in an appropriate specialty (e.g., dermatology, plastic surgery, etc.).

One image set, containing only the frontal view, will be paired as follows:

- Set 1 (treated subjects only): Photograph 1 (baseline) vs. Photograph 2 (Day 90 or Day 180 post-treatment);
- Set 2 (untreated individuals only): Photograph 1 ("baseline") vs. Photograph 2 (post-baseline).

Photograph 1 will be identified, and the independent evaluators will be blinded to the random distribution of treated versus untreated status of the comparator Photograph 2 (i.e., Day 90 or Day 180 post-treatment among treated subjects or post-baseline for untreated individuals).

For each image set, blinded evaluators will assess each photograph and will be asked the following: "Using Photograph 1 as a reference, which of the following best characterizes the change in aesthetic appearance observed in the comparator Photograph 2: Improvement or No Improvement."

Improvement will be declared if at least two blinded evaluators indicate "Improvement" for the comparator photograph.

Additional information on the methodological plan, detailing photograph collection through subsequent presentation to blinded evaluators, will be provided in a supporting document, developed collaboratively between the sponsor and the photography vendor.

This assessment will be proctored by the central photography vendor.

CCI

[redacted]

CCI

[redacted]

11.2.2 Safety Assessments

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

[redacted]

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

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

[redacted]

CCI

[redacted]

[redacted]

11.2.3 Additional Data Collected

Data for other assessments will be collected as follows:

- Demographics and other baseline characteristics, including FST[redacted], height, and weight;

[redacted]

- Urine pregnancy tests (only if subject is of childbearing potential);
- Number of treatment lines administered, stratified by region and transducer;
- Relevant medical history/concomitant diseases; and
- Concomitant therapies.

12 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

12.1 Definition of an Adverse Event (AE)

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

Note:

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

12.1.1 Details of an AE

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

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 participation in the trial.

12.1.2 Reporting and Handling of an AE

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

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

In cases of an SAE (defined in Section 12.2), the investigator must also complete an SAE Report Form and report it to the sponsor within 24 hours, as described in Section 12.2.2.

12.1.3 Severity Grading for an AE

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

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

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

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

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

12.1.4 Causal Relationship of an AE with an Investigational Medical Device

An AE is considered to be "related" to IMD or the treatment procedure if a causal relationship between the IMD or the treatment procedure and an AE is at least reasonably possible. In this case, the non-serious event is considered an adverse device effect (ADE; Section 12.3). If the event is serious, it is a serious adverse device effect (SADE; Section 12.4).

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

12.1.5 Outcome Categories for an AE

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

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

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

12.2 Definition of a Serious Adverse Event (SAE)

An SAE is an adverse event that:

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

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical study protocol (CSP), without serious deterioration in health, is not considered an SAE.

12.2.1 Details of an SAE

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

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

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

- suitable action had not been taken; or
- intervention had not been made; or
- if circumstances had been less fortunate

should be categorized as an SAE and reported accordingly.

12.2.2 Reporting and Handling of an SAE

All SAEs that occur during the clinical study period, whether considered to be related to an IMD or not, must be reported via telephone or e-mail, and an SAE Report Form should be submitted to the sponsor immediately of knowledge of the event. Further reporting details will be outlined in a separate document.

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

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

The investigator must report SAEs to Merz as defined in Section 12.2 and the site's IEC/IRB per their reporting guidelines.

Within 10 working days after Merz first receives notice of the SAE, Merz Product Safety will conduct an evaluation of the SAE and report the results of such evaluation to regulatory agencies, IECs/IRBs, and investigators, as applicable.

The investigator must supply further supporting information, and a detailed SAE description is an integral part of this supporting information. Follow-up SAE reports should be sent without delay to the sponsor as an SAE Report Form (marked as a "follow-up" report), and the eCRF has to be updated accordingly to avoid discrepancies. The SAE has to be followed until the SAE is resolved/recovered or a plausible explanation is available. The SAE will be followed 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 study database. Following database close for the study, any ongoing SAEs will be followed until resolution or stabilization under the responsibility of the investigators per their standard of care.

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

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

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

12.3 Definition of an Adverse Device Effect (ADE)

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

Note:

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

12.4 Definition of a Serious Adverse Device Effect (SADE)

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

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

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

12.4.2 Definition of an Unanticipated Adverse Device Effect (UADE)

A UADE is defined as follows:

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

12.5 Definition of Device Deficiency

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

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

12.6 Definition of Technical Complaint

A technical complaint, also referred to as a product complaint, is an apparent or suspected deficiency of a product in which the product does not meet its specification (e.g., console error, transducer failure, handpiece malfunction).

Note: The term “technical complaint” is synonymous with the term “device deficiency”. The term device deficiency is used in this study.

12.6.1 Reporting and Handling of Device Deficiencies

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

For reporting of device deficiencies:

- For device deficiencies related to a specific subject's treatment, a Device Deficiency eCRF must be completed and submitted by the investigational site, irrespective of the seriousness of the case.
- For device deficiencies related to a specific subject's treatment, a Device Deficiency eCRF must be completed and submitted by the investigational site, irrespective of whether the complaint led to an AE. The investigator will attempt to evaluate if the device 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.
- 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. SAE Report Forms should be sent to Merz Product Safety for processing (Section 12.2.2).
- If a device deficiency is not related to a specific subject (e.g., damaged transducer or handpiece occurring prior to the subject's visit), the investigator should complete a paper device deficiency form (e.g., Device Technical Complaint Form), instead of the eCRF, and send to the sponsor within 24 hours to both their clinical study representative as well as to the Merz Technical Complaint Department for processing using the following email address: devicehelp@merz.com. If needed, technical complaint support can be reached at 877-858-4372.

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

[redacted]

12.8 Reporting of Pregnancy

Any pregnancy that starts during the clinical study must be reported by the investigator to the sponsor within 24 hours of learning of its occurrence. 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. Pregnancies and pregnancy follow-up should be reported on a Pregnancy Form; this form should be submitted to the contacts referenced in Section 12.2.2. In addition, each pregnancy has to be reported on the AE eCRF (i.e., as a non-serious AE due to device exposure before or during pregnancy). If subjects become pregnant during the study, they will remain enrolled for safety follow-up.

13 STATISTICAL METHODS

This section describes the statistical analyses foreseen at the time of study 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 interim closure of the study database. If needed, the SAP will be updated before database close at the end of the study.

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

13.1 Estimation of Sample Size

A responder rate of 70% is assumed for the proportion of subjects with improvement from baseline to Day 90, as defined by the correct selection of the Day 90 standardized, photographic images by two of three independent, blinded evaluators. Monte-Carlo simulations were conducted to obtain sample sizes of evaluable subjects required to achieve an improvement rate of $\geq 65\%$ and lower bound of 1-sided 95% confidence interval above 50%. To achieve this threshold with $\geq 85\%$ power, a sample size of 80 evaluable subjects will be required. Assuming a maximum attrition of 10 subjects, approximately 90 subjects will be enrolled. In Stage 1, 10 subjects will be enrolled, while all other subjects will be enrolled in Stage 2. Because a sample size of 80 subjects who complete the full Ultherapy treatment session is required, study enrollment will continue until the required number of treated subjects is achieved.

13.2 Randomization

No randomization procedures for treatment allocation will be used in this study.

13.3 Populations for Analysis

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

- The Safety Population (SP) includes all subjects who are enrolled and are treated with the Octave System.
- The Intent-to-Treat (ITT) population consists of all subjects who are enrolled.
- The Per Protocol (PP) population consists of all subjects in the ITT population who complete the full Ultherapy treatment session using the Octave System and do not have a major protocol violation.

13.4 Analysis of Study Data

Adequate descriptive statistics will be provided for each effectiveness and safety evaluation as provided in Section 7.2. Numeric variables will be summarized by number of observations, mean, standard deviation, min, median, max (i.e., metric statistics). Categorical variables will be summarized by frequencies and percentages per category where the denominator will be chosen according to the adequate analysis population (i.e., frequency statistics). Ordered categorical data will be summarized by quantitative and frequency statistics. Variables will be analyzed as absolute data and as change from baseline, as applicable. Shift tables, confidence limits (95%, two-sided), and descriptive p-values will be given, where appropriate.

All data captured in the eCRF will be listed.

13.4.1 Effectiveness Analyses

Unless otherwise specified, all effectiveness endpoints will be summarized for the ITT population.

13.4.1.1 Primary Effectiveness Endpoint

The proportion of subjects fulfilling the primary endpoint will be described by frequency statistics for the ITT subset.

Effectiveness is established if the point estimate is ≥ 65% and the lower bound of the one-sided 95% Wilson CI is > 50%.

[redacted]

Sensitivity analyses will comprise:

- PP population with observed cases,
- ITT with observed cases, and
- ITT with missing value treated as no improvement.

[redacted]

Gain or loss of ≥ 2 BMI units from screening to Day 90 will be considered a major protocol deviation. Subjects with gain or loss of ≥ 2 BMI units from screening to Day 90 will be excluded from PP population. The following subgroups will be defined by the change in body weight from screening to Day 90:

- Subjects in ITT population with gain of ≥ 2 BMI units;
- Subjects in ITT population with loss of ≥ 2 BMI units; and
- Subjects in ITT population with change of < 2 BMI units.

Primary endpoint with observed cases will be analyzed in all subgroups, as defined above, with more than five subjects.

13.4.1.2 Secondary Effectiveness Endpoint

Note: Secondary endpoint will be assessed only among subjects reconsented for extended study participation.

The proportion of subjects fulfilling the secondary endpoint will be described by frequency statistics for the ITT subset, including the one-sided 95% Wilson CI.

[redacted]

CCI

[redacted]

13.4.2 Safety Analyses

All safety evaluations will be summarized for observed values in the SP.

13.4.2.1 Secondary Safety Endpoint

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

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

An overall summary of AEs will be provided for the following:

- Any AEs;
- Any non-TEAEs;
- Any TEAEs;
- Any treatment-related TEAEs;
- Any serious TEAEs, and
- Any TEAEs leading to discontinuation.

Incidences will be provided for the following classes of AEs:

- TEAEs by MedDRA preferred term (PT) and system organ class (SOC);
- TEAEs by PT;
- TEAEs by maximum severity, maximum duration, and combination of both by PT;
- Related TEAEs by PT and SOC; and
- Serious TEAEs by PT and SOC,
- Related serious TEAEs by PT and SOC.

Moreover, incidences of TEAEs, by PT and SOC, will be provided for the following subgroups: Race and FST (I, II, III versus IV, V, VI).

Listings for all AEs, as well as subsets including AEs leading to discontinuation, related SAEs, and deaths, will be provided. Treatments discontinued due to pain and device deficiencies will also be listed.

CCI [redacted]

CCI

[redacted]

13.4.3 Other Subject Data

All demographic, baseline characteristics, and subject disposition data will be presented using standard descriptive statistics. Demographic data will be summarized for the SP and also for the ITT subset if differences exist between the two populations.

Frequencies of concomitant treatments will be given based on different Anatomical Therapeutic Chemical (ATC) Classification System code levels for the SP. Indications for concomitant therapies will not be coded and will only be listed.

Medical history and concomitant diseases will be coded using the MedDRA dictionary and reported by SOC and PT levels for the SP. Extent of exposure (lines applied by region and transducer) will be summarized.

13.5 Special Statistical/Analytical Issues

13.5.1 Subject Discontinuation and Missing Data

The methods intended for handling a missing primary or secondary effectiveness endpoint are described in Section 13.4.1.1 and Section 13.4.1.2, respectively.

[redacted]

For the remaining endpoints, observed cases will be analyzed, unless otherwise specified.

13.5.2 Interim Analysis

In Stage 1, an initial cohort of 10 subjects will be enrolled. An interim database close and interim safety analysis of the first 10 subjects treated in Stage 1 will be conducted. This Stage 1 analysis will contain Week 2 safety data for the first 10 subjects treated. Safety analyses will be performed on the SP. Effectiveness data will not be included in the interim analysis.

Continuation to Stage 2 will be paused during evaluation of the Week 2 safety data from the first 10 subjects treated. All 10 subjects enrolled in Stage 1 will participate until Stage 1 study end, for a maximum duration of 90 days (± 7 days).

The interim analysis is only intended to obtain safety data for the first 10 subjects treated before starting recruitment for Stage 2. The interim analysis is not proposed to modify the study design, statistical analyses, or sample size, or for study termination, as this is not an adaptive study design. Since no effectiveness data are analyzed at interim, the interim analysis will not compromise the integrity of the study's effectiveness data, and it will not bias the final effectiveness analysis.

14 ADMINISTRATIVE PROCEDURES

14.1 Study Monitoring

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

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

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

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

14.2 Data Quality Assurance

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

14.2.1 Standardization Procedures

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, evaluations, and validation methods). Standardized photography methods will be detailed in a separate photography user manual.

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

14.2.2 Data Management

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

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

Photographs will be archived by the central photography vendor in a system separate from the database (see Section 14.3). [redacted] photo ratings by independent, blinded investigators will be transferred electronically to the data management CRO. Checks will be performed to ensure plausibility and completeness of these data. The data management activities and photograph processing will be delegated to [redacted] CROs [redacted]

After all necessary data for the interim safety analysis of the first 10 subjects enrolled in Stage 1 have been entered and cleaned, an interim database close will be performed.

The database will be closed after all subjects have completed their Day 90 visit and again after completion of their Day 180 visit. Hence, after all applicable data are entered, monitored, and verified, and all queries are solved, the database will be closed. After database close at Day 90, the relevant pages will remain locked for further data entry and/or update. If data changes are needed after database close, they will be documented according to the respective SOP. The same requirements apply for the Day 180 database lock.

For the final analysis, after all data are entered and all queries are resolved, the database will be closed again. If any data changes are required after database close, these changes will be documented according to the respective SOP.

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

14.2.3 Data Review and Clarification Procedures

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

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

All data required by this study protocol, except photography ratings [redacted], are to be entered into a sponsor-validated database of eCRFs.

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

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

Entries from questionnaires completed by the subject will be entered into the eCRF by study personnel. If corrections in the questionnaires are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date and initial the correction. The investigator should not make any changes to these documents.

14.2.4 Auditing

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

14.3 Record Retention

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

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

- Copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies);
- Copies of all relevant correspondence between the investigator and the monitor, and between the investigator and the sponsor;
- Copies of any photographs;
- Copies of IMD receipt forms and device inventory forms; and
- Copies of safety information reported during the investigation and submitted by the sponsor.

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

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

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements, with the minimum retention time being the longest of those times dictated by institutional requirements, local laws or regulations, or the sponsor's standard procedures. The investigator must notify the sponsor in the event of any changes to archival arrangements due to withdrawal of the investigator's responsibility for keeping study records to ensure that suitable arrangements for the retention of study records are made.

14.4 Publication Policy

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

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

The investigator agrees that the results of this study may be used for submission to national or international registration and supervising authorities. The sponsor may disclose the information obtained during the study to regulatory authorities or other personnel as

required. If necessary, the sponsor may disclose the names, contact information, and qualifications of all investigators as well as their roles in the study. Upon completion of the study, publication or disclosure of the study results is to follow the terms contained in the sponsor's SOP.

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

14.5 Financial Disclosure

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

14.6 Investigator Compliance

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

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

If an immediate deviation from the protocol is required to eliminate an immediate hazard to subjects, the investigator must contact the sponsor or assigned CRO, if possible, to discuss the planned course of action. The investigator must thoroughly document any departure from the protocol and submit appropriate documentation to the sponsor without delay.

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16 APPENDICES