Ultherapy

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CLINICAL PROTOCOL NUMBER ULT-146

NON-INFERIORITY STUDY OF THE SAFETY AND EFFICACY OF ULTHERAPY® USING STANDARD VERSUS SIMULINES TRANSDUCERS AT A REDUCED ENERGY LEVEL FOR PATIENT COMFORT

CONFIDENTIAL – PROPRIETARY INFORMATION

DATE: 02/06/2017

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SIGNATURE PAGE

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Protocol Title:	Non-Inferiority Study of the Safety and Efficacy of Ultherapy® Using Standard versus Simulines Transducers at a Reduced Energy Level for Patient Comfort
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SPONSOR AGREEMENT

Ulthera, Inc. (hereinafter "Study Sponsor") maintains responsibility for the ongoing safety of this clinical trial involving the evaluation of the Ulthera System®. Study Sponsor will promptly notify all investigators, the responsible IRB(s), and the regulatory authorities of any findings from ongoing trial monitoring activities that could adversely affect the safety of subjects, impact the conduct of the clinical study, or alter the IRB's approval to continue the study, specifically within 5 working days of making an Unanticipated Adverse Device Effect (UADE) determination or 15 working days after first receiving notice of the UADE, within 10 days for Serious Adverse Event reports, and at least annually for routine reports. In the event that participant safety could be directly affected by study results after the study has ended, Study Sponsor will notify all investigators of these results to enable investigators to consider informing participants as soon as possible or at least within one year of study closure.

INVESTIGATOR AGREEMENT AND CERTIFICATION

I hereby agree to participate in this clinical trial sponsored by Study Sponsor. I agree to conduct this investigation according to the requirements of the protocol provided by the Study Sponsor and in accordance with Part 812 and other applicable FDA regulations, and regulations of other relevant regulatory authorities and conditions imposed by the reviewing Institutional Review Board (IRB) or Ethics Committee (EC). I agree to ensure that appropriate informed consent is obtained from all subjects prior to inclusion in this study. I also agree to supervise all testing of the device involving human subjects. I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time.

I understand that this investigation will be monitored by the Study Sponsor and/or a designee employed by the Study Sponsor. This monitoring will involve periodic inspection of my investigational site and ongoing review of the data that is submitted by me to the Study Sponsor. All study data will be entered within 1 week after the targeted study follow-up visit. I am also aware that I may be inspected by a representative of the relevant regulatory authorities, including the United States Food and Drug Administration, to verify compliance with applicable regulations related to clinical research on human subjects.

My current curriculum vitae and the curriculum vitae of physicians/licensed practitioners at this institution who will participate as co-investigators/sub-investigators in this study will be provided to the Study Sponsor. These curriculum vitae will include the extent and type of our relevant experience with pertinent dates and locations.

I certify that I have not been involved in an investigation that was terminated for non-compliance at the insistence of the Study Sponsor, the IRB or EC, or other regulatory authorities. I agree to provide the Study Sponsor sufficient, accurate financial disclosure information. I also agree to update financial disclosure information if any relevant changes occur during the investigation and for one year following the completion of the study.

I understand that this study protocol and the trial results are confidential, and I agree not to disclose any such information to any person other than a representative of the Study Sponsor or the relevant competent authorities without the prior written consent of the Study Sponsor.

Accepted by:

Principal Investigator Signature	Date
Principal Investigator Name	
Co-/Sub-Investigator Signature	Date
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PROTOCOL SYNOPSIS

Company Name:	Ulthera, Inc.
Protocol Number:	ULT-146
Protocol Title:	Non-Inferiority Study of the Safety and Efficacy of Ultherapy® Using Standard versus Simulines Transducers at a Reduced Energy Level for Patient Comfort
Investigational Device:	Ulthera® System
Development Phase:	Pivotal
Study Objective:	The objective of this study is to demonstrate that the safety and efficacy of Simulines transducers at Energy Level 2 [EL2] is not inferior to treatment with Standard transducers at Energy Level 2 [EL2] in order to limit the energy level of both types of transducers to a maximum of EL2 for lift indications. To fulfill this objective we will be using the same treatment depths and regions treated as those used in the pivotal study that supported the submental/ neck clearance, but at EL2 instead of Energy Level 4 [EL4]. Simulines transducers deliver 2 lines of treatment per pulse (push of the button) versus Standard transducers which deliver 1 line of treatment per pulse.
Study Design:	Prospective, randomized, double blinded, multi-site (up to 8 sites), parallel arm, non-inferiority trial
Number of Subjects:	N = Up to 260 randomized and treated subjects; subjects enrolled may be greater than subjects treated. A minimum of 20 subjects and a maximum of 45 subjects will be enrolled at each site.
Study Treatment Groups:	Enrolled subjects will be randomized to one of two treatment groups. Subjects will be blinded to their assigned treatment group. All randomized subjects will receive a single, dual depth lower face and neck Ultherapy® treatment. Group A will receive treatment of the lower face and neck with Standard transducers at EL2. The number of treatment lines in each region currently requiring an odd number of lines will be rounded up to even numbers for equivalency in lines of treatment between Standard and Simulines treatment groups (e.g. if 15 standard lines are required in a region on the standard map then this will be rounded up to 16 lines to match the 16 lines required on the Simulines map). Group B will receive treatment of the lower face and neck with Simulines transducers at EL2. Subjects randomized to Group A will receive an Ultherapy® treatment to the lower face and neck with a total minimum pulse count of 672 pulses (+5%) at the 4.5mm and 3.0mm depths using Standard transducers. Energy levels for each transducer will be set to EL2: • DS 4-4.5 at 0.9J with pitch of 1.5mm and 17 TCPs per line • DS 7-3.0 at 0.30J with pitch of 1.1mm and 23 TCPs per line Subjects randomized to Group B will receive a comparable treatment with a total minimum pulse count of 336 pulses (+5%) using the Simulines transducers at the 4.5mm and 3.0mm depths. Energy levels for each transducer will be set to EL2: [redacted]
Subject Population:	Adults between 30 and 70 years of age who meet the inclusion/exclusion criteria.
Inclusion Criteria:	1. Male or female, age 30 to 70 years. 2. Subject in good health. 3. BMI of ≤30. 4. Skin laxity in the area(s) to be treated as determined by trained physician assessors. 5. Willingness to avoid excessive or prolonged exposure to sunlight, tanning

	booths, sun lamps, or UV light sources. 6. Willingness to apply study provided sunscreen (Neocutis Micro-Day Rejuvenating Cream) daily until study exit to help limit sun exposure. 7. Willingness to avoid or periodically stop use of Sunless Tanners (washout period of two weeks prior to each study visit is required). 8. Understands and accepts the obligation not to undergo any other procedures in the areas to be treated through the follow-up period 9. Willingness to avoid non-emergent dental procedures in the 3 weeks prior to/ post treatment. 10. Willingness and ability to comply with protocol requirements, including returning for follow-up visits and abstaining from exclusionary procedures for the duration of the study. 11. Subjects of childbearing potential must have a negative urine pregnancy test result and must not be lactating at the Screening Visit and be willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study. Women will not be considered of childbearing potential if one of the following conditions is documented on the medical history: a. Postmenopausal for at least 12 months prior to study; b. Without a uterus and/or both ovaries; or c. Bilateral tubal ligation at least six months prior to study enrollment. 12. Absence of physical or psychological conditions unacceptable to the investigator. 13. Willingness to refrain from use of aspirin, Ibuprofen, Naproxen or any other NSAID prior to study treatment and chronic use during the entire post-treatment study period. Washout period, if chronic user, for 4 weeks prior to the study treatment. After study treatment is completed, limited acute NSAID use, i.e., a maximum of 2-3 doses in any 2 week period, is allowed if needed. 14. Willingness and ability to provide written consent for study-required photography and adherence to photography procedures (i.e., removal of jewelry and makeup). 15. Willingness and ability to provide written informed consent and HIPAA authorization prior to performance of any study-related procedure.
Exclusion Criteria:	1. Presence of an active systemic or local skin disease that may affect wound healing. 2. History of Bell's Palsy. 3. History of chronic or frequently recurring episodic (recurrent episode in past 12 months) autoimmune diseases such as Multiple Sclerosis, Crohn's Disease, Psoriasis, Myasthenia Gravis, Lambert-Eaton Syndrome that has required immune suppressant therapy (such as biologic drug or corticosteroid treatment). 4. Palpable thyroid lesion, lymphadenopathy, or other pathological changes within the treatment area. 5. History of skin cancer in the areas to be treated, basal cell nevus syndrome, or jaw cysts. 6. Known allergy or sensitivity to Ibuprofen. 7. Severe solar elastosis. 8. BMI > 30. 9. Significant changes in weight (e.g. more than 5 pounds) over the past 6 months or anticipated significant changes in weight or diet over the course of the study.

10. Pregnant within the past year.
11. Excessive subcutaneous fat in the area(s) to be treated.
12. Excessive skin laxity in the area(s) to be treated as determined by trained physician assessors.
13. Significant scarring in the area(s) to be treated that would interfere with assessing results.
14. Open wounds or lesions in the area(s) to be treated.
15. Severe or cystic acne on the area(s) to be treated.
16. Active implants (e.g., pacemakers or defibrillators), or metallic implants in the treatment areas (dental implants not included).
17. Inability to understand the protocol or to give informed consent.
18. Microdermabrasion, or prescription level glycolic acid treatment to the treatment area(s) within two weeks prior to study participation or during the study.
19. Marked asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin in the area(s) to be treated.
20. History of chronic drug or alcohol abuse.
21. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study device.
22. Subjects who anticipate the need for surgery or overnight hospitalization during the study.
23. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
24. Concurrent enrollment in any study involving the use of investigational devices or drugs.
25. Current smoker or history of smoking in the last five years.
26. Current user of any nicotine-containing products, e.g., e-cigarettes, Nicorette gum, nicotine patches, etc.
27. History of the following cosmetic treatments in the area(s) to be treated:
    a. Any energy based device (RF, MFU, etc.) procedure for skin tightening within the past year;
    b. Injectable filler of any type within the past:
        i. 12 months for Hyaluronic acid fillers (e.g. Restylane)
        ii. 12 months for Ca Hydroxylapatite fillers (e.g. Radiesse)
        iii. 24 months for Long Lasting Hyaluronic acid (e.g. Voluma) and Poly-L-Lactic acid fillers (e.g. Sculptra)
        iv. Ever for permanent fillers (e.g. Silicone, ArteFill)
    c. Neurotoxins within the past six months (neuromodulators are allowed in the glabella and forehead, not allowed in the temples, crow's fee or anywhere below the lateral canthus);
    d. Fractional and fully ablative resurfacing laser treatment within the past two years;
    e. Nonablative, rejuvenative laser or light treatment within the past six months;
    f. Surgical dermabrasion or deep facial peels within the past two years;
    g. Facelifts, neck surgery (e.g. thyroid, neck lifts, neck liposuction, etc.) within the past two years;
    h. Micro needling within the past year;
    i. Kybella, Coolsculpting, or Mesotherapy within the past two years; or
    j. Any history of contour threads.

28. History (in the prior year) or current use of the following prescription medications:

	a. Accutane or other systemic retinoids within the past six months; b. Initiation of topical retinoids within the past 6 months or throughout the course of the study; c. Antiplatelet agents/Anticoagulants (Coumadin, Heparin, Plavix); d. Systemic steroids including prednisone; e. Dermal regulators of collagen; f. Initiation of bioidentical hormones or HGH within the past 6 months or throughout the course of the study; or g. Psychiatric drugs that in the investigators opinion would impair the subject from understanding the protocol requirements or understanding and signing the informed consent.
Treatment Outline:	1. Screening: a. Screen for general inclusion/exclusion criteria; b. Obtain informed consent; c. Perform screening photography (2D photography; 5 views: Front, Right 45◦; Left 45◦; Right 90◦, and Left 90◦) to confirm eligibility; d. Up to 4 weeks ±7days washout period, if required, for chronic NSAID use. 2. Baseline Visit (The screening visit may not be more than 14 days prior to Baseline. Greater than 14 days between screening and baseline visits will require that the subject be re-screened to confirm enrollment eligibility.): a. Confirm eligibility for participation; b. Obtain pregnancy screen (if applicable); and c. Complete baseline evaluations, including demographics, height, weight, BMI, Fitzpatrick Skin Type, and medical history; d. Perform baseline photography: i. Screening 2D photographs (5 views) will be used if of acceptable quality as Baseline photos. ii. Quantificare 3D imaging system will also be used at up to 3 study sites and in up to 135 subjects. The 3D images will only be used for marketing purposes. iii. Capture adverse events (if necessary). 3. Treatment Visit (The baseline visit may not be more than 14 days prior to Treatment. Greater than 14 days between baseline and treatment visits will require that the subject be re-screened to confirm enrollment eligibility.): a. Subject treatment; and b. Obtain post-treatment 2D images (3 views: Front, Right 90◦, and Left 90◦). 4. Post-treatment telephone contacts: a. 3±1 days - Capture adverse events b. 7±2 days - Capture adverse events 5. Follow-up Visits for efficacy evaluation: a. 90±14 days i. Obtain images (2D photographs, 5 views; 3D photographs with Quantificare imaging system at applicable site(s)); ii. Obtain Global Aesthetic Improvement Scale (CGAIS and SGAIS); iii. Obtain Patient Satisfaction Questionnaire. b. 180± 21 days i. Obtain images (2D photographs, 5 views; 3D photographs with Quantificare imaging system at applicable site(s));

	ii. Obtain Global Aesthetic Improvement Scale (CGAIS and SGAIS). c. 365±30 days i. Obtain images (2D photographs, 5 views; 3D photographs with Quantificare imaging system at applicable site(s)); ii. Obtain Global Aesthetic Improvement Scale (CGAIS and SGAIS); and iii. Obtain pregnancy screen (if applicable). iv. Obtain blinding assessments: Clinician and Subject Blinding Questionnaires. 6. Follow-up Visits for safety evaluation: a. Immediately post-treatment i. Assess for adverse events. b. All follow-up visits i. Assess for adverse events.
Primary Endpoint:	1. Efficacy will be assessed based on quantitative measurements of neck and submental lift at 90 days post-treatment compared to baseline. Subject response is defined as ≥20 mm^2 reduction in 2D submental area from baseline. (Note: this is the same methodology and success criteria which supported the FDA clearance of the submental/neck lift indication for this device, Attachment A.) Simulines transduces will be considered non-inferior to Standard transducers using a non-inferiority margin of 15% between the two arms of the trial. The study was powered based on the expected response rate of 73% as seen in the pivotal trial supporting the neck/submental lift indication FDA clearance K121700. The observed response rate of the prior pivotal trial (73%) was higher than the minimum response rate required (65%) for success of the supporting trial.
Secondary Endpoints:	1. Subject response as measured by quantitative improvement measurements of submandibular and submental lift at 180 and 365 days post-treatment compared to baseline. 2. Comparison of improvement in overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs at 90, 180 and 365 days post-treatment compared to baseline. 3. Assessment of mean change from baseline to 90 days post treatment on the validated, Merz Jawline Grading Scale (MJGS) by independent masked evaluators. 4. Quantificare 3D imaging of up to 135 study subjects to assess volumetric changes from baseline compared to 90, 180, and 365 days post-treatment. 5. Patient satisfaction and patient reported improvement at 90 days post-treatment. 6. Comparison of average treatment times using Simulines transducers compared to average treatment times using Standard transducers. 7. Comparison of average pain scores using a validated Numeric Rating Scale to assess subjects' treatment-related comfort level with Simulines transducers versus Standard transducers. 8. Subject Global Aesthetic Improvement Scale (SGAIS) results assessing overall aesthetic improvement at 90, 180 and 365 days post-treatment. 9. Clinician Global Aesthetic Improvement Scale (CGAIS) results assessing overall aesthetic improvement at 90, 180, and 365 days post-treatment.
Other Data Collected:	Prior to treatment, the subject's medical history will be reviewed, a urine pregnancy test will be performed (if applicable), and a physical examination will be conducted. At each subsequent visit, the subject will be queried about adverse events and changes in

	concomitant medications, and the treatment area will be visually examined. An additional pregnancy screening test will be performed at the 365-day follow-up visit (if applicable).
Study Duration:	Given five months for recruitment, the anticipated study duration is seventeen months.

STUDY OVERVIEW

Evaluation / Procedure	Screening Visit	Baseline Visit+	Treatment Visit+	Telephone Contact Day 3 ± 1D Day 7 ± 2D	Day 90±14 Follow-up	Day 180±21 Follow-up	Day 365±30 Follow-up
Informed Consent	√						
Eligibility Assessment (Inclusion/Exclusion[1])		√[4]					
Demographics and Medical History		√					
Pregnancy Screening^		√					√
Skin Examination[2]		√	√				
Treatment of Face and Neck			√				
Collection of Treatment Time			√				
Subject Assessment of Pain[3]			√				
2D images; 3D Images (at applicable site(s))	√	√[4]	√[5]		√	√[6]	√[6]
Masked Qualitative Assessments					√	√	√
Jawline Scale		√			√		
Patient Satisfaction Questionnaire					√		
Clinician Global Aesthetic Improvement Scale - CGAIS					√	√	√
Subject Global Aesthetic Improvement Scale - SGAIS					√	√	√
Clinician Blinding Questionnaire							√
Subject Blinding Questionnaire							√
Adverse Event Assessment		*	*	*	*	*	*

+Baseline and Treatment Visits may be separate visits or combined into one visit.

*Complete AE Form when necessary

^ Pregnancy:

a. If a subject becomes pregnant after the Baseline visit and after study treatment, the subject should continue to be followed.
b. If a subject becomes pregnant after the Baseline visit but before study treatment, the subject should be exited from the study.

NOTES:

1. Baseline Form
2. Baseline Clinical Observations (Pre-Treatment) or Clinical Safety and Adverse Events (Post-Treatment and at Follow-up Intervals).
3. Subject Pain Assessment Scale using a validated Numeric Rating Scale. Pain scores should be obtained following each region treated and for each transducer used. Record the average pain score for the entire region treated.
4. Baseline assessment and pre-treatment photos should be obtained within 14 days of study treatment. Screening photos may be used as Baseline photos.
5. Post-treatment images taken 30-60 minutes following Ultherapy© treatment for documentation of any immediate post-treatment AEs.
6. Images taken on this visit, but not a primary endpoint for efficacy.

List of Acronyms and Definitions

Term	Definition
AE	Adverse Event
CGAIS	Clinician Global Aesthetic Improvement Scale
CV	Curriculum Vitae
EC	Ethics Committee
Elastosis	Degeneration of the elastic tissues
ETE	Expected Treatment Effect
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCPs	Good Clinical Practices
IFC	Instructions for Use
IRB	Institutional Review Board
MEEI	Massachusetts Eye and Ear Infirmary, Harvard Medical School
MJGS	Merz Jawline Grading Scale
NRS	Numeric Rating Scale for pain assessment
Pitch	The distance between subsequent thermal coagulations points in a line of treatment
PSQ	Patient Satisfaction Questionnaire
Pulse	Energy delivered by one push of the button on the device handpiece
RF	Radiofrequency
Rhytidectomy	Mini-facelift
Serious Adverse Event	An adverse event that results in or contributes to death or is life threatening. See Section 7.4 for more detail.
Adverse event severity	The intensity of an adverse event, which can range from mild to moderate to severe. See Section 7.6 for more detail.
SGAIS	Subject Global Aesthetic Improvement Scale
Simulines Transducers	Transducers that deliver two lines of thermal coagulation points simultaneously per pulse or push of the button.
SMAS	Superficial Musculo-Aponeurotic System; terminal branches of sensory nerves of the face run in the layer above the Superficial Musculo-Aponeurotic System.
Standard Transducers	Transducers that deliver one line of thermal coagulation points per pulse or push of the button
TCP	Thermal coagulation point
TMM	Tissue Mimicking Material
UCSD	University of California at San Diego
Ulthera® System	Ulthera® Ultrasound System and Accessories
US	Ultrasound
Walk Distance	The distance the transducer is manually moved between delivery of treatment lines.

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1. INTRODUCTION

1.1 DEVICE NAME AND INDICATIONS FOR USE

The Ulthera® System is indicated for use as a non-invasive dermatological aesthetic treatment to lift the eyebrow, lax submental (under the chin) and lax neck tissues as well as improvement of wrinkles and lines in the décolleté. The Ulthera® System in conjunction with the Ulthera DeepSEE transducer integrates high-resolution ultrasound imaging with ultrasound therapy. The Ulthera® System has been demonstrated to be safe and effective in previous clinical trials as a non-invasive treatment to produce improvement in the areas of treatment through sub-dermal tissue coagulation and tightening, and for ultrasonic visualization of depths up to 8 mm below the surface of the skin and sub-dermal tissue.

Ulthera has recently developed a new type of transducer, a Simulines transducer, which delivers two treatment lines of thermal coagulation points (TCPs) at once (simultaneously) per pulse (push of the button) instead of a single line of TCPs delivered by one pulse of a Standard transducer in order to improve the efficiency of delivering an Ultherapy® treatment. Bench top and animal testing has confirmed that the thermal coagulation points (TCPs), or micro-coagulation zones, within a line of treatment created by the Simulines transducers are cumulatively equivalent to those in a line of treatment created by the Standard commercialized transducers. In other words, the amount of tissue affected within a line of similar transducers is roughly equivalent. The clinical trial described in this protocol will evaluate clinical outcomes associated with this non-invasive treatment to improve skin laxity and tightening using the Standard transducers compared to the Simulines transducers. Comfort levels will be measured by collection of pain scores during the treatment, efficacy will be primarily measured by quantitative submental and neck lift measures (**Attachment A**), and treatment efficiency will be measured by the time it takes to deliver a Standard versus Simulines treatment. Other secondary efficacy measures include masked assessments, the Global Aesthetics Improvement Scale (GAIS) (**Attachments B and C**) to assess overall aesthetic improvement will be collected from the investigator, sub-investigator, or qualified study staff member and subject, subject satisfaction and subject reported improvement measured by a Patient Satisfaction Questionnaire (**Attachment D**).

1.2 BRIEF AGING BACKGROUND AND TREATMENT OVERVIEW

Normal aging results in characteristic changes in the skin and underlying connective tissue of the face, generally described as the "Aging Face Syndrome." These biologic changes, which include facial rhytids and laxity, result from cutaneous photo damage after repeated sun exposure and other factors, such as genetic predisposition. These factors change the three-dimensional structure of skin collagen (e.g. crosslinking and altered 3D structure) leading to a loss of its inherent elasticity. In order to develop a treatment plan customized for each subject, a thorough knowledge of basic skin anatomy is essential (**Figure 1.2-1**). Treatment is then based on an individual's clinical presentation.

FIGURE 1.2-1: SKIN ANATOMY

Various energy delivery devices have been developed in an effort to treat facial rhytids and skin laxity [1, 2]. These devices create thermal injuries which in turn induce a "wound healing" response, in which fibroblasts synthesize and produce new collagen. This collagen remodeling process is the crucial step in facial rejuvenation. Several types of laser and radiofrequency treatment techniques have been used to treat the superficial skin layers (e.g. CO_2, Smoothbeam, Cooltouch, Thermage, etc.) and have demonstrated surface level thermal-induced "skin tightening effects".

Ultrasound is an energy modality that can be focused to penetrate deeper in the tissue and cause micro thermal coagulative zones. This approach avoids the undesirable post-treatment effects observed with laser treatment of the superficial layers [3, 4]. Focused ultrasound heating has several potential advantages over lasers and radiofrequency (RF) devices in that it is able to confine heating to small focal regions with a combination of precision and depth not possible with lasers or RF devices.

1.3 Mechanism of Action

The Ulthera® System images and delivers focused ultrasound energy to specific soft tissue layers under the superficial layer of epidermis. Ultrasound treatment creates focal micro-coagulation zones in the skin, causing thermally induced contraction of tissue and a "wound-healing" response to stimulate the formation of new tissue and collagen, and to cause a skin-tightening/wrinkle-reduction effect.

The device is designed and configured to produce small micro-coagulation zones in the mid to deep reticular layer of dermis and sub-dermis per line of treatment (approximately $1mm^3$), while sparing overlying papillary dermal and epidermal layers of skin. The device also incorporates an ultrasound imaging capability to evaluate the skin tissue and avoid structures such as bone and large vessels.

1.4 Device Overview

The Ulthera System currently consists of three primary components (**Figure 1.4-1**):

1. Control unit with integrated touch screen;
2. Handpiece; and
3. One of eight removable transducers.(Six of these transducers are currently cleared and two are under investigation)

FIGURE 1.4-1: PRIMARY COMPONENTS

Use of the Ulthera® System is a computer-driven treatment that provides guidelines for energy delivery to specific anatomical regions per approved indication. The transducer can be used to image the treatment area prior to and during the treatment stage using the DEEPSEE® imaging function. A treatment protocol is initiated by selecting the desired treatment region. The suggested line count for energy delivery per appropriate transducer is then displayed. The face and neck are divided into the following regions: upper third of face (hairline to cheekbone), lower two thirds of face (cheekbone to jawline), and neck (submental, submandibular, and lower). In this protocol the lower face and neck (submental and submandibular) regions will be treated as done in the pivotal study leading to our neck/submental (underneath the chin) lift indication.

The anatomical depth of focal tissue heating is fixed and determined by the set focus depth of a given transducer, and to a lesser extent by the ultrasound power and exposure duration. In general, higher frequencies are used for more superficial tissue effect compared to lower frequencies[5].

Six transducers are commercially available two of which will be used in this trial (DS 4-4.5 and DS 7-3.0). Two Simulines transducers (DS 4-4.5S and DS 4-3.0S) are in development and will be evaluated in this clinical trial. The transducers differ in the frequency of ultrasound energy emitted: 4 MHz, 7 MHz, and 10 MHz as well as differing treatment depths (4.5mm, 3.0mm, or 1.5mm, respectively). All transducers can image tissue up to 8mm in depth. Transducer capabilities are shown in **Table 1.4-1**.

TABLE 1.4-1: TRANSDUCER TYPES

Transducer Types	Treatment Frequency	Default Energy Level	Treatment Depth	Image Depth
DS 4-4.5	4 MHz	[redacted]	4.5mm	0 to 8 mm
DS 7-3.0	7 MHz	[redacted]	3.0mm	0 to 8 mm
DS 7-3.0*N*	7 MHz	[redacted]	3.0mm	0 to 8 mm
DS 7-4.5	7 MHz	[redacted]	4.5mm	0 to 8 mm
DS 10-1.5	10 MHz	[redacted]	1.5mm	0 to 8 mm
DS 10-1.5*N*	10 MHz	[redacted]	1.5mm	0 to 8 mm
DS 4-4.5S	4 MHz	[redacted]	4.5mm	0 to 8 mm
DS 4-3.0S	4 MHz	[redacted]	3.0mm	0 to 8 mm

Energy Level is the total energy output for a line of TCPs expressed in Joules (J). The number of Joules is determined by the Acoustic Power in Watts (W) and the length of time (T, in seconds) the power is on/being delivered to create an entire line of TCPs. The equation to determine the energy level (EL) for a TCP in Joules is W x T = J. The Ulthera system has capability of 4 different energy levels to be used commercially. The desire is to limit the lift indications to the lower two energy levels for patient comfort. When using the Ulthera System, clinicians will continue to have the ability to adjust the energy settings between two pre-set energy levels programmed for each transducer based on their clinical judgement for the treatment being delivered. Energy Level 2, EL2, (shown in **Table 1.4-1**) will be used in this study. Other energy levels will not be allowed in this trial. The stated default energy is the total energy delivered to the patient to form a singular TCP when using the standard transducers. The total energy stated for the Simulines transducer is the total energy delivered to the patient to form two TCPs. As such, each TCP created using the Simulines transducer receives half of the stated energy per TCP. Simulines transducers exploit a particular method of constructive acoustic interference to achieve two simultaneous locations of peak spatial intensity, thereby creating two TCPs at the same depth, at once.

In the case of the DS 4-3.0S, [redacted]

Each treatment region is treated in a lined pattern ("line" is a row of TCPs). Using the Standard transducer, multiple lines of treatment are delivered as the transducer is advanced 2-3 mm within the region, and multiple passes of the region are utilized until all treatment lines have been delivered for that region, and treatment of the region is complete. [redacted] Because the Simulines transducer is delivering two simultaneous lines, the transducer must be advanced twice as far (4-6mm). This distance between energy deliveries is called the walk distance. Multiple passes of this wider walk distance are utilized until all lines are delivered within a region. The user then moves to the next region of treatment. Treatment patterns under the current protocol are described in Section 5.1.

1.5 Preclinical Studies

The Ulthera® System has been evaluated in a series of preclinical studies to demonstrate that the device performs as intended, meets its specifications, and is safe and suitable for clinical use. These studies verified and validated electrical safety, electromagnetic compatibility, mechanical properties, and software performance. In addition, functional preclinical studies were conducted to verify and validate device performance.

Preclinical studies were conducted at Massachusetts Eye and Ear Infirmary – Harvard Medical School (MEEI) and Ulthera laboratories using a porcine skin model, which has a similar skin structure to human. These studies demonstrated that the Ulthera® System reliably creates small, micro-coagulative zones in the reticular dermis layer.

Similar findings have been confirmed in human cadaver studies at the University of California at San Diego (UCSD, MEEI, and Wellman Lab – Harvard Medical School). Cadaver skin tissue was treated using the Ulthera® System at frequencies of 4-7 MHz. The focal depths of the 4 MHz transducer were 4.5mm and 6mm. The focal depths of the 7MHz transducer were 3mm and 4.5mm. These studies further demonstrated that the Ulthera® System reliably creates small, well-confined micro-coagulative zones.

1.6 Clinical Studies

Three clinical studies have been conducted using the Ulthera® System: a clinical safety study at MEEI (Protocol Number 05-06-032), a pivotal study at Northwestern University in Chicago (Protocol Number 1253-014, IDE G060261), and a clinical safety and

effectiveness Study at the University of Texas Southwestern Medical Center (UTSW) (Protocol Number 00000404). During these three studies the Ulthera® System was extensively used, and safe and efficacious energy delivery protocols were established. A fourth study, a pivotal, multi-center, safety and effectiveness study (Protocol Number ULT-129, IDE G120004) evaluated the safety and efficacy of the Ulthera System to achieve improvement of lines and wrinkles of the décolleté. The FDA has granted at least five (5) clearances of the Ulthera System which included the use of transducers at energy level 4 (EL-4). The transducers to be used under this clinical protocol will be used at energy level 2 (EL2).

1.6.1 Clinical Safety Study at MEEI

A prospective, open-label clinical safety study was conducted at MEEI in 15 subjects who were scheduled to undergo a limited rhytidectomy (mini-facelift) procedure (Protocol Number 05-06-032). The study was approved by the MEEI Human Studies Committee (the Institutional Review Board [IRB]), and all subjects signed the informed consent document. The objective of this clinical study was to confirm the conclusion that the Ulthera® System provides controlled thermal micro-coagulative zones in the dermis while sparing the epidermis. Safety was assessed in terms of skin inflammation, pain, adverse events, and histology.

Subjects were treated with the Ulthera® System either approximately 24 hours before or 4 to 12 weeks before undergoing a mini-facelift. The investigator performed treatment using the Ulthera® System according to the instructions provided in the protocol and based upon the treatment plans verified and validated in prior preclinical testing. The investigator selected the transducer and then performed one of three treatment plans on the portion of the face and neck that would be subsequently excised during the mini-facelift.

Fifteen subjects were treated; 7 subjects underwent the facelift surgery within 24 hours following treatment with the Ulthera® System and 8 subjects underwent the facelift surgery within 4 to 12 weeks after treatment. During treatment, 1,300 ultrasound exposure pulses were delivered using three different transducers, including the 7-4.5mm, 7-3.0mm, and 4-4.5mm transducers. There was no disruption to the epidermis noted in any subject, no adverse events noted, and no delayed adverse sequelae to the treated skin. The skin tissue was excised during the mini-facelift procedure either immediately or 4 to 12 weeks after treatment. The tissue was frozen, sectioned, and stained for gross and histopathology evaluation. Histopathology analysis of acute samples of skin tissue treated with the Ulthera® System (within 24 hours) showed thermal coagulative zones below the skin epidermis with complete epidermal preservation. Histopathology was also performed on the tissue excised from those subjects who underwent a delayed facelift (4 to 12 weeks following treatment with the Ulthera® System). No definitive findings of discrete coagulative changes were observed in the delayed cases, and there were no findings of extensive fibrous tissue or tissue scarring.

The Ulthera® System was determined to be safe for delivery of targeted, precise, and consistent regions of thermal coagulation in the dermis and subcutaneous tissues while sparing of the epidermis.

1.6.2 Clinical Safety and Effectiveness Study at Northwestern University

A prospective, open-label clinical study was conducted at Northwestern University (Protocol Number 1253-014, G060261). The study was approved by the IRB at Northwestern University, and all subjects signed the informed consent document. The objectives of this clinical study were to: 1) demonstrate the safety of the Ulthera® treatment and 2) achieve eyebrow elevation resulting from tissue coagulation and tightening. Thirty-five subjects were enrolled in the study. Enrolled subjects were of either sex over the age of 21, who had a desire to obtain an improvement of eyebrow elevation and had chosen to receive an Ultherapy® treatment. Enrollment was open to all skin types (Fitzpatrick I-VI).

Subjects were treated with the Ulthera® System on their faces and necks. The investigator performed treatments using the Ulthera® System according to the instructions provided in the protocol. The investigator selected the transducer and treatment plan for each individual subject. Thirty-five subjects were treated using the Ulthera® System and all three transducers were used. All subjects were followed for over 90 days to assess safety and effectiveness.

All subjects completed and tolerated the procedure well. There was no disruption to the epidermis observed in any subject and no adverse events were observed. Further there was no evidence of skin hyper- or hypo-pigmentation in subjects for up to 10 months following treatment.

A masked, clinical assessment of eyebrow position was performed by evaluating pre- and post-treatment images to determine efficacy. Subjects underwent standardized photographic evaluations on Day 0, pre-treatment, and Day 90, post-treatment. Three board-certified physicians assessed the eyebrow height and characteristics by reviewing in a randomized order the Day 0 and Day 90 images of each subject. The cumulative result of the three masked reviewers was an 85.7% "Improved" evaluation for the 35 subjects. Twenty-four subjects treated with the Ulthera® System completed a Patient Satisfaction Survey at 8 to 10 months post-treatment. The survey demonstrated that 75% of the subjects were either satisfied or very satisfied with improvement in their eyebrow position after the Ulthera® treatment. In addition, 75.7% of the subjects demonstrated a measurable improvement in eyebrow height at Day 90 post-treatment.

This clinical study using the Ulthera® System to treat the face and neck demonstrated safe and efficacious delivery of ultrasound energy. The thermal coagulative tissue effect in skin resulted in a clinically significant improvement of the eyebrow position in the majority of subjects, while preserving the epidermis.

1.6.3. Clinical Safety and Effectiveness Study at The University of Texas Southwestern Medical Center (UTSW)

An open-label, prospective, non-randomized, clinical trial was conducted at UTSW (Protocol Number 00000404) to examine the safety and efficacy of the Ulthera® System for treating the lower face, submentum and neck to achieve improvement in submental and neck skin laxity. The study was approved by the IRB at UTSW, and all subjects signed the informed consent document. The objectives of this clinical study were to: 1) demonstrate the safety of the Ulthera® treatment and 2) demonstrate improvement in jawline definition and submental laxity by quantitative assessment of the amount of visible tissue lift.

In this study, 70 subjects *(ranging in age from 35 to 58 years)*, received Ultherapy® *(low density treatment of 290 lines)* on the lower face and submentum with both the 7 MHz 3.0 mm transducer and either the 7 MHz 4.5 mm transducer or the 4 MHz 4.5 mm transducer, as determined by the investigator for each subject. Improvement in jawline definition and submental laxity was assessed at 90 days by quantitative assessment of the amount of visible tissue lift seen in the photographs and comparison of pre- and post-treatment photographs by three masked clinician reviewers. All subjects were followed for over 90 days to assess safety and effectiveness. Additionally, patient satisfaction was assessed at 90 and 180 days post-treatment.

Study subjects were assessed for adverse events immediately post-procedure, and then at 60, 90 and 180 days. A total of seven adverse events were reported; however, only three were considered device/procedure related *(welting of the skin within the treated area)*. All of the events resolved with no residual sequelae. The three device related adverse events were considered mild in nature.

The quantitative assessment for the right and left side of the face yielded a response rate of 72.9% *(51 out of 70)* of subjects that had a visible tissue lift of ≥ 20.0 mm^2 of the submental area when comparing the pre-treatment and 90-day post-treatment photos. The average area of tissue lift in the study subjects who were considered responders were 71.97 mm^2 and 71.69 mm^2 for their left and right sides, respectively. The quantitative results were consistent for both the right and left side of the face. Additionally, 84.3% of subjects who were identified as responders by quantitative assessment were also identified as responders in the qualitative masked assessment. Based on the masked assessment conducted by three experienced clinicians of pre- and 90-day post-treatment photograph pairs, 68.6% of subjects had improvement *(visibly observable tissue lift)* in the submental area *(beneath the chin)* and neck. The patient satisfaction questionnaire indicated that 67% of the subjects saw an improvement in face and neck characteristics.

This study demonstrated that Ultherapy© is safe and efficacious for the improvement in submental *(beneath the chin)* and neck laxity and supported FDA clearance of the submental/neck lift indication the device received. The efficacy of the treatment using EL2 energy levels is expected to produce a similar 72.9% response rate.

1.6.4 Prospective, Multi-center, Pivotal Trial Evaluating the Safety and Effectiveness of the Ulthera System for Improvement in Lines and Wrinkles of the Décolleté

An open-label, prospective, non-randomized multi-center clinical trial was conducted evaluating the safety and efficacy of the Ulthera System to achieve improvement of lines and wrinkles of the décolleté. The clinical study's protocol was approved under IDE G120004 (Protocol Number ULT-129) for enrolling up to 130 female subjects between the ages of 35-60 at up to four clinical sites with a 90 and 180-day follow up. The Fabi-Bolton Scale, a published validated scale, was prospectively defined to evaluate wrinkle improvement. However, successful validation of the Fabi-Bolton Scale during the clinical trial could not be accomplished due to kappa scores for both intra-rater and inter-rater reproducibility being low. Therefore, the primary endpoint was changed from the Fabi-Bolton Scale to a post-hoc retrospective masked assessment of pre and 180-day post treatment photographs. There were no pre-specified success criteria of the masked assessment established at the beginning of the clinical trial. In addition to masked assessment, there was also an unmasked assessment called the Clinician Global Aesthetic Improvement Scores (CGAIS). Finally, patient satisfaction questionnaires were also measured to assess improvement.

Upon analysis of all the photographs used in the clinical study, 54 of 108 day 180 photos were identified as having inconsistencies in photo quality (changes in lighting, color, focus, patient positioning, cropping, etc.). Therefore a sub-set analysis was conducted using the primary endpoint of masked assessment on the remaining 54 day 180 evaluable photo sets that were deemed the most consistent in photo quality. The results of the sub-set analysis demonstrated improvement of lines and wrinkles based on masked assessment of pre- and post-treatment photographs in 36 of 54 (~67%) evaluable subjects with the most consistent photo quality after one Ultherapy© treatment 180 days post-treatment. Subjects' overall aesthetic improvement was based on CGAIS assessment by the study clinician. Subjects rated at some degree of improvement *(very much improved, much improved or improved)* were 76% and 65% at 90 and 180 days, respectively. Patient satisfaction questionnaires (PSQ), completed at 90 and 180 days post-treatment captured whether subjects were satisfied with their Ultherapy© treatment and if they noticed improvement in their décolleté area. At 90 days, 62% and 81% of the subjects were satisfied with their Ultherapy© treatment and noticed improvement in their décolleté area, respectively. This response continued through 180 days post-treatment, where 65% and 85% of the subjects were satisfied and noticed improvement in their décolleté area, respectively. Device safety was demonstrated as there were no serious adverse events (SAEs) or unanticipated adverse device effects (UADEs) related to treatment with the Ulthera System. Of the adverse events, all but two were mild. Only two events were moderate, one of which was not device-related. All events resolved.

This study demonstrated that Ultherapy© is safe and efficacious for the improvement of lines and wrinkles of the décolleté.

1.7 Simulines Pre-clinical Studies Background

An important component of Ultherapy® treatment is patient comfort. [redacted] There are 3 main factors contributing to patient comfort, each of which have been considered when developing the Simulines transducer: 1) spatial (distance), 2) temporal (time) and 3) patient fatigue.

Spatial refers to the proximity of the TCPs to each other and to nerve endings within the tissue. The higher the number of TCPs delivered the more closely packed the TCPs will be in a given area and the more likely that TCPs will be close to or on top of nerve endings. In a face/neck treatment following the conventional guideline, the space between lines is approximately 2-3mm. The clinician advances the transducer this distance between each delivery of a treatment line. [redacted] As with the Standard transducers, if patient discomfort is experienced the space between the treatment lines may be increased, i.e., the clinician advances the transducer a greater walk distance, and delivery of the recommended number of treatment lines may be completed in multiple passes within an area. Clinicians will be asked to advance the Simulines transducer approximately twice the distance that the Standard transducer is advanced. When delivering a treatment using a Simulines transducer, the same number of treatment lines are delivered, but with only half as many instances of delivering pulses of energy. [redacted]

The second factor is the temporal component. It is known from experience with over 500,000 treatments globally, that the more time allowed between pulses of energy the more comfortable the patient is. If a patient is comfortable, a clinician is able to deliver the treatment lines quickly with little time between pulses. If the patient is experiencing discomfort the time between pulses may be increased. This ability to control timing of pulses by the clinician is similar between Standard transducers and Simulines transducers. If a patient is uncomfortable the clinician may pause between each Simulines pulse to increase comfort. This temporal component is also important when looking at the delivery of a single line. At the beginning of delivery of a line of treatment, it is common for a patient to not feel much discomfort; however, patients have experienced a heightened sensation as the last few TCPs in that treatment line are delivered. This has been referred to as "wind up". Each TCP is delivered in 21-50 milliseconds with up to 23 TCPs per treatment line, and it is theorized that there is a delay in perceiving discomfort. C-fiber nerve conduction velocity is 0.5-20 meters/second which may explain the heightened sensation as the delivery of each treatment line progresses/time passes. [redacted]

The third component of discomfort is patient fatigue. It is also known after years of clinical experience with this device that the longer it takes to complete a treatment the more discomfort a patient experiences. It is expected that the Simulines transducer will have a positive impact on patient fatigue, and therefore a positive impact on treatment-related comfort. Delivering two treatment lines at once is expected to shorten treatment time and reduce patient fatigue.

In addition, damage of tissue causes the release of neuropeptides, kinases, substance P, etc. which activate nerve endings. It is expected that local release of these substances around TCPs created by either single or double lines will <u>not</u> be different.

[redacted]

1.7.1 Simulines Transducer Overview

The Simulines transducers, referred to as DS 4-4.5S and DS 4-3.0S, are capable of delivering two treatment lines simultaneously at the same focal depth. [redacted]

[redacted]

The energy settings were validated against the conventional treatment in tissue mimicking material, porcine muscle, and in-vivo porcine skin. [redacted] The safety of the derived DS 4-4.5S and DS 4-3.0S energy settings was evaluated in a 96 hour porcine survival dosage study by monitoring the animal for evidence of erythema, edema, and contusion on the skin surface after treatment. Each energy setting of each transducer, DS 4-4.5S and DS 4-3.0S, was evaluated by itself and in combination with the other Simulines transducer at the same energy level. The survival data suggested little to no skin surface effects when treating with the derived DS 4-4.5S, and DS 4-3.0S energy settings. Any skin effects resolved within hours which is equivalent to conventional transducers.

Based on this body of data, the DS 4-4.5S transducer, produces TCPs similar in size to the Standard DS 4-4.5 transducer. The DS 4-3.0S transducer produces a line of TCPs that affect a similar amount of tissue compared to the Standard DS 7-3.0 transducer but requires only 20 TCPs versus 23 TCSs with the DS 7-3.0mm transducer.

1.7.2 transducer Laboratory Testing

Simulines DS 4-4.5 and DS 4-3.0 transducers were built and tested in a number of mediums for evaluation of the amount of coagulated tissue produced by a line. This section summarizes the evaluation performed. Table 1.7.2-1 and 1.7.2-2 describes energy settings used during testing. This study will be carried out using Standard and Simulines transducers set at Energy Level 2 [EL2]. [redacted]

[redacted]

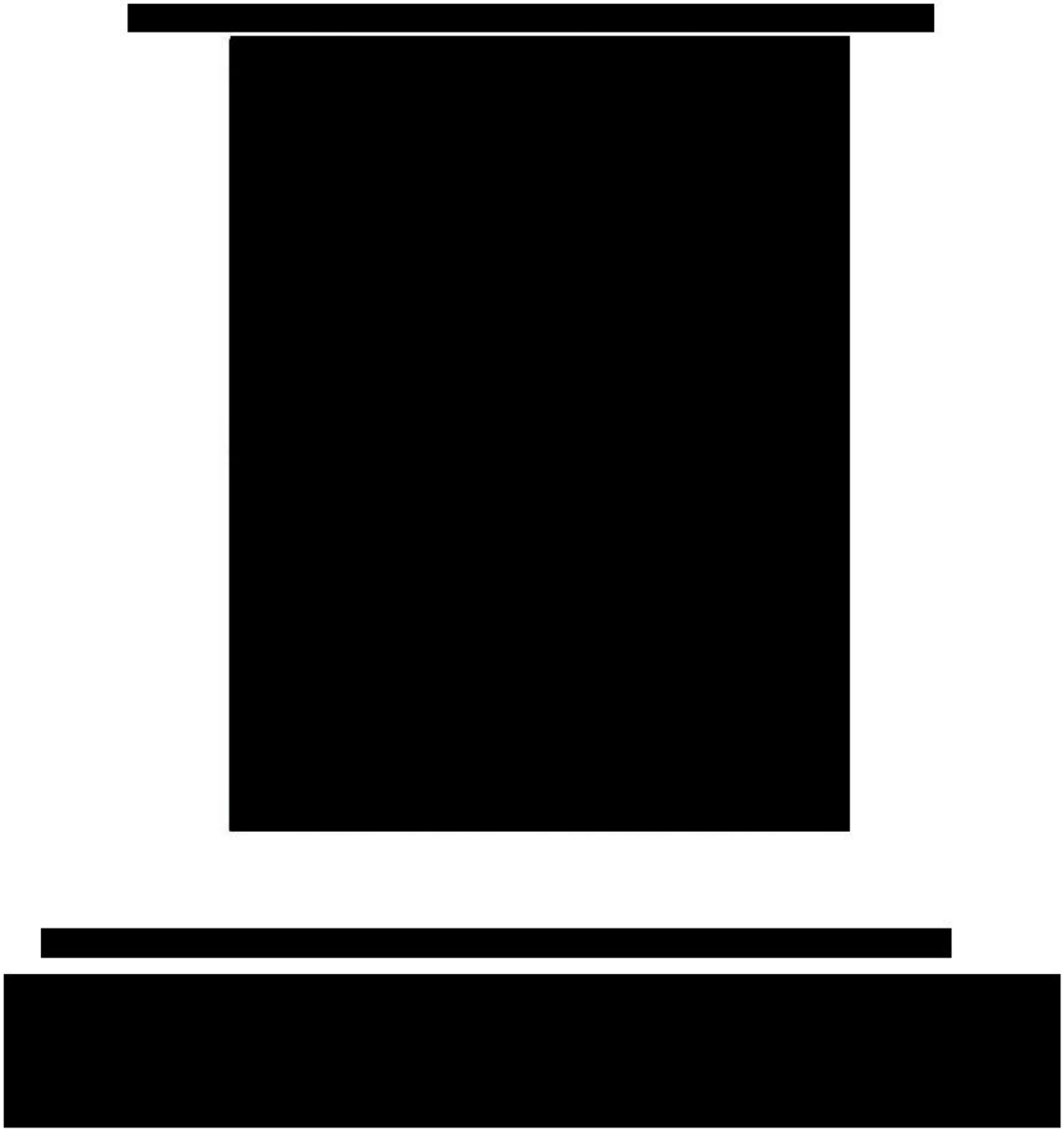
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

2. Study Objective and Design

2.1 Study Objective

The objective of this study is to demonstrate that the safety and efficacy of Simulines transducers at Energy Level 2 [EL2] is not inferior to treatment with Standard transducers at Energy Level 2 [EL2] in order to limit the energy level of both types of transducers to a maximum of EL2 for lift indications. To fulfill this objective we will be using the same treatment depths and regions treated as those used in the pivotal study that supported the submental/ neck clearance, but at EL2 instead of Energy Level 4 [EL4]. Simulines transducers deliver 2 lines of treatment per pulse (push of the button) versus Standard transducers which deliver 1 line of treatment per pulse.

2.2 Type and Design of Study

This study is a prospective, randomized, double blinded multi-center, parallel arm, non-inferiority clinical trial to be conducted at up to eight clinical sites. Up to 260 subjects (a minimum of 20 subjects and a maximum of 45 subjects at each clinical site) will be enrolled and treated if they meet the inclusion/exclusion criteria and provide written informed consent, in a staged study initiation. In an initial stage, 15 subjects will be randomized and treated at one clinical site. Following FDA approval of a safety report, enrollment at all study sites will commence. Investigator or qualified study staff member will assess baseline criteria prior to treatment to confirm eligibility.

Enrolled subjects meeting all entrance criteria and confirmed eligible for study treatment will be randomized into one of two treatment groups. Subjects will be treated using the Ulthera® System by the study investigator, sub-investigator or qualified study staff member. Subjects and the study clinician performing efficacy assessments should remain blinded to the assigned treatment group. Standardized images will be taken prior to treatment, following treatment (30 to 60 minutes post-treatment), and during each follow-up visit using Quantificare software, a head positioning device, and a 2D digital imaging system. Quantificare 3D imaging (at up to 3 sites on up to 135 study subjects, these images will be used for marketing purposes only) will also be used to assess volumetric changes. The 3D photograph and volumetric change data will only be used for marketing purposes, not as a support for the primary efficacy analysis. Baseline assessments and pre-treatment images should be obtained within 14 days of the study treatment.

2.3 Duration of Study

It is expected that recruitment for this study will take 5 months. After the treatment visit, subjects will be followed for a total duration of 365-days. Therefore, the anticipated total duration of the study is approximately 17 months.

3. Study Procedures

3.1 Schedule of Assessments at Each Study Visit

Table 3.1-1 provides an overview of the subject screening procedure, baseline evaluation, treatment plan, and follow-up requirements.

TABLE 3.1-1: SCHEDULE OF ASSESSMENTS

Evaluation / Procedure	Screening Visit	Baseline Visit+	Treatment Visit+	Telephone Contact Day 3 ± 1D Day 7 ± 2D	Day 90±14 Follow-up	Day 180±21 Follow-up	Day 365±30 Follow-up
Informed Consent	√						
Eligibility Assessment (Inclusion/Exclusion[1])		√[4]					
Demographics and Medical History		√					
Pregnancy Screening^		√					√
Skin Examination[2]		√	√				
Treatment of Face and Neck			√				
Collection of Treatment Time from System Treatment Log			√				
Subject Assessment of Pain[3]			√				
2D images; 3D Images (at applicable site(s))	√	√[4]	√[5]		√	√[6]	√[6]
Masked Qualitative Assessments					√	√	√
Jawline Scale		√			√		
Patient Satisfaction Questionnaire					√		
Clinician Global Aesthetic Improvement Scale - CGAIS					√	√	√
Subject Global Aesthetic Improvement Scale - SGAIS					√	√	√
Clinician Blinding Questionnaire							√
Subject Blinding Questionnaire							√
Adverse Event Assessment		*	*	*	*	*	*

+Baseline and Treatment Visits may be separate visits or combined into one visit.

^ Pregnancy:

a. If a subject becomes pregnant after the Baseline visit and after study treatment, the subject should continue to be followed.
b. If a subject becomes pregnant after the Baseline visit but before study treatment, the subject should be exited from the study.

*Complete AE Form when necessary.

NOTES:

1. Baseline Form
2. Baseline Clinical Observations (Pre-Treatment) or Clinical Safety and Adverse Events (Post-Treatment and at Follow-up Intervals).
3. Subject Pain Assessment Scale using a validated Numeric Rating Scale. Pain scores should be obtained following each region treated and for each transducer used. Record the average pain score for the entire region treated.
4. Baseline assessment and pre-treatment photos should be obtained within 14 days of study treatment. Screening photos may be used as Baseline photos
5. Post-treatment images taken 30-60 minutes following Ultherapy© treatment for documentation of immediate post-treatment AEs.
6. Images taken on this visit, but not a primary endpoint for efficacy.

4. SUBJECT SELECTION AND PRE-TREATMENT

The study population will consist of males and females between 30 and 70 years of age who have chosen to participate in this clinical trial as evidenced by execution of the informed consent document.

4.1 PRE-TREATMENT RECRUITING/SCREENING

Subjects who meet the enrollment criteria will be selected by the principal investigator from the study site's patient database and/or who are recruited using IRB approved recruitment materials. Study site personnel will explain the design and purpose of the study to potential study subjects. Subjects interested in participating will visit the study site where informed consent will be obtained.

4.2 INFORMED CONSENT

Written informed consent will be obtained from all subjects before any study-related procedures, including any pre-treatment screening procedures, are performed. Investigators, or qualified study staff member, may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent. Informed consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research.

Investigators have ethical and legal responsibilities to ensure that the protocol is clearly explained to each subject considered for enrollment in the study. Compliance with this requirement should be documented on a written Informed Consent Form approved by the reviewing IRB. Each Informed Consent Form will include the elements required by FDA regulations in 21 CFR Part 50.

The IRB-approved Informed Consent Form will be signed by the subject and the investigator, sub-investigator, clinical research coordinator, or other qualified study staff member obtaining consent. The subject will be given a copy of the signed Informed Consent Form. The investigator will keep the original on file. A copy will be placed in the subject's chart.

4.3 ELIGIBILITY

4.3.1 INCLUSION CRITERIA

Subjects must meet all of the following criteria for study enrollment:

1. Male or female, age 30 to 70 years.
2. Subject in good health.
3. BMI ≤30.
4. Skin laxity in the area(s) to be treated as determined by trained physician assessors.
5. Willingness to avoid excessive or prolonged exposure to sunlight, tanning booths, sun lamps, or UV light sources.
6. Willingness to apply study provided sunscreen (Neocutis Micro-Day Rejuvenating Cream) daily until study exit to help limit sun exposure.
7. Willingness to avoid or periodically stop use of Sunless Tanners (washout period of two weeks prior to each study visit is required).
8. Understands and accepts the obligation not to undergo any other procedures in the areas to be treated through the follow-up period.
9. Willingness to avoid non-emergent dental procedures in the 3 weeks prior/post treatment.

10. Willingness and ability to comply with protocol requirements, including returning for follow-up visits and abstaining from exclusionary procedures for the duration of the study.
11. Subjects of childbearing potential must have a negative urine pregnancy test result and must not be lactating at the Screening Visit and be willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study. Women will not be considered of childbearing potential if one of the following conditions is documented on the medical history:
    a. Postmenopausal for at least 12 months prior to study;
    b. Without a uterus and/or both ovaries; or
    c. Bilateral tubal ligation at least six months prior to study enrollment.
12. Absence of physical or psychological conditions unacceptable to the investigator.
13. Willingness to refrain from use of aspirin, Ibuprofen, Naproxen or any other NSAID prior to each study treatment and chronic use during the entire post-treatment study period. Washout period, if chronic user, for 4 weeks prior to the study treatment. After study treatment is completed, limited acute NSAID use, i.e., a maximum of 2-3 doses in any 2 week period, is allowed if needed.
14. Willingness and ability to provide written consent for study-required photography and adherence to photography procedures (i.e., removal of jewelry and makeup).
15. Willingness and ability to provide written informed consent and HIPAA authorization prior to performance of any study-related procedure.

4.3.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria:

1. Presence of an active systemic or local skin disease that may affect wound healing.
2. History of Bell's Palsy.
3. History of chronic or frequently recurring episodic (recurrent episode in past 12 months) autoimmune diseases such as Multiple Sclerosis, Crohn's Disease, Psoriasis, Myasthenia Gravis, Lambert-Eaton Syndrome that has required immune suppressant therapy (such as biologic drug or corticosteroid treatment).
4. Palpable thyroid lesion, lymphadenopathy, or other pathological changes within the treatment area.
5. History of skin cancer in the areas to be treated, basal cell nevus syndrome, or jaw cysts
6. Known allergy or sensitivity to Ibuprofen.
7. Severe solar elastosis.
8. BMI > 30.
9. Significant changes in weight (e.g. more than 5 pounds) over the past 6 months or anticipated significant changes in weight or diet over the course of the study.
10. Pregnant within the past year.
11. Excessive subcutaneous fat in the area(s) to be treated as determined by trained physician assessors.
12. Excessive skin laxity in the area(s) to be treated.
13. Significant scarring in the area(s) to be treated that would interfere with assessing results.
14. Open wounds or lesions in the area(s) to be treated.
15. Severe or cystic acne on the area(s) to be treated.
16. Active implants (e.g., pacemakers or defibrillators), or metallic implants in the treatment areas (dental implants not included).
17. Inability to understand the protocol or to give informed consent.
18. Microdermabrasion, or prescription level glycolic acid treatment to the treatment area(s) within two weeks prior to study participation or during the study.
19. Marked asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin in the area(s) to be treated.

20. History of chronic drug or alcohol abuse.
21. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study device.
22. Subjects who anticipate the need for surgery or overnight hospitalization during the study.
23. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
24. Concurrent enrollment in any study involving the use of investigational devices or drugs.
25. Current smoker or history of smoking in the last five years.
26. Current user of any nicotine-containing products, e.g., e-cigarettes, Nicorette gum, nicotine patches, etc.
27. History of the following cosmetic treatments in the area(s) to be treated:
    a. Any energy based device (RF, MFU, etc.) procedure for skin tightening within the past year;
    b. Injectable filler of any type within the past:
        i. 12 months for Hyaluronic acid fillers (e.g. Restylane)
        ii. 12 months for Ca Hydroxylapatite fillers (e.g. Radiesse)
        iii. 24 months for Long Lasting Hyaluronic acid (e.g. Voluma) and Poly-L-Lactic acid fillers (e.g. Sculptra)
        iv. Ever for permanent fillers (e.g. Silicone, ArteFill)
    c. Neurotoxins within the past six months (neuromodulators are allowed in the glabella and forehead, not allowed in the temples, crow's fee or anywhere below the lateral canthus);
    d. Fractional and fully ablative resurfacing laser treatment within the past two years;
    e. Nonablative, rejuvenative laser or light treatment within the past six months;
    f. Surgical dermabrasion or deep facial peels within the past two years;
    g. Facelifts, neck surgery (e.g. thyroid, neck lifts, neck liposuction, etc.) within the past two years
    h. Micro needling within the past year;
    i. Kybella, Coolsculpting, or Mesotherapy within the past two years; or
    j. Any history of contour threads.
28. History (in the prior year) or current use of the following prescription medications:
    a. Accutane or other systemic retinoids within the past six months;
    b. Initiation of topical retinoids within the past 6 months or throughout the course of the study;
    c. Antiplatelet agents/Anticoagulants (Coumadin, Heparin, Plavix);
    d. Systemic steroids including prednisone;
29. Dermal regulators of collagen;
30. Initiation of bioidentical hormones or HGH within the past 6 months or throughout the course of the study; or
31. Psychiatric drugs that in the investigators opinion would impair the subject from understanding the protocol requirements or understanding and signing the informed consent.

After subjects have provided informed consent and met the inclusion/exclusion criteria, the study procedures described in the following section will be performed. Subjects can be enrolled in the study and treated according to this protocol on the same day.

4.4 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented in writing (i.e., subject signs an Informed Consent Form), but who does not receive a study treatment because of failure to meet all of the eligibility criteria. Screen failure subjects will be included in the total number of subjects enrolled (i.e., all subjects consented), but not counted towards the total subjects treated.

4.5 Subject Randomization and Treatment Group Assignment

At the Treatment visit, only qualified study subjects (i.e., signed the IRB-approved consent form and confirmed eligible) will be randomly assigned according to a computer-generated 1:1 randomization to receive Ultherapy® treatment using either the Simulines or Standard transducers.

Randomizations will be stratified by site and will use randomly selected blocks of size 4 and 6 and will be generated by an electronic database in a reproducible fashion and will be provided to the site by electronic data capture the point that randomization occurs.

Enrolled subjects will be randomized to one of two treatment groups. Subjects and the study clinician performing efficacy assessments should remain blinded to the assigned treatment group. All randomized subjects will receive a single, dual depth lower face and neck Ultherapy® treatment. Group A will receive treatment with Standard transducers at EL2. The number of treatment lines in each region currently requiring an odd number of lines will be rounded up to an even number for equivalency between Standard and Simulines (e.g. if 15 lines are required in a region on the Standard transducer treatment map then this will be rounded up to 16 lines to match the 16 lines required on the Simulines map). Group B will receive treatment with Simulines transducers at EL2.

Subjects randomized to Group A will receive an Ultherapy® treatment to the lower face and neck with a total minimum pulse count of 672 pulses (+5%) at the 4.5mm and 3.0mm depths using Standard transducers. Energy levels for each transducer will be set to EL2:

- DS 4-4.5 at 0.9J with pitch of 1.5mm and 17 TCP's per line
- DS 7-3.0 at 0.30J with pitch of 1.1mm and 23 TCP's per line

Subjects randomized to Group B will receive a comparable treatment with a total minimum pulse count of 336 pulses (+5%) using the Simulines transducers at the 4.5mm and 3.0mm. Energy levels for each transducer will be set to EL2:

[redacted]

The assigned treatment group should be documented on the appropriate study-specific data form and study log.

4.6 Study Images

At all sites, the images in the study will be obtained using the 2D Quantificare digital photo system and software for image collection, storage, and analysis. To ensure consistent, reproducible study photos from baseline photographs to the follow-up photographs, Quantificare photography guidelines and procedures must be followed, see **Attachment H.** Site personnel will be trained on these guidelines at the Investigator Meeting. The following photographs should be obtained at each study visit, for each imaging system used:

- Screening/Baseline 2D photographs, capturing 5 views: Frontal View; Right and Left Lateral (90◦); Right and Left Oblique (45◦);
- Immediate Post-treatment Standard 2D photographs, capturing 3 views: Frontal View; Right and Left Lateral (90◦).
- 90 Day Follow-Up Standard 2D photographs, capturing 5 views: Frontal View; Right and Left Lateral (90◦); Right and Left Oblique (45◦);

- Day 180 Follow-Up Standard 2D photographs, capturing 5 views: Frontal View; Right and Left Lateral (90◦); Right and Left Oblique (45◦);
- Day 365 Follow-Up Standard 2D photographs, capturing 5 views: Frontal View; Right and Left Lateral (90◦); Right and Left Oblique (45◦);

Subjects' Screening/Baseline images are considered the pre-treatment comparator images. Screening/Baseline images may be taken within 14 days prior to study treatment. ***Subject photos must be reviewed prior to study treatment to ensure proper subject selection and photographic quality.***

At up to 3 sites (in up to 135 subjects), additional images will be obtained using a 3D Quantificare system, see **Attachment I** (these images will be used only for marketing purposes). To ensure consistent, reproducible study photos from baseline to follow-up, Quantificare's photography guidelines and procedures must be followed, see **Attachment H.** Site personnel will be trained on these guidelines on an individual basis by Quantificare prior to study enrollment.

In order to carefully control the positioning of the subject for reproducible photos at each time point the Quantificare positioning device will be utilized at all sites for the all photographs, both 2D and 3D. The system is composed of a pair of thin/light weight glasses equipped with lasers that subjects will wear during the photo session. The lasers will be projected on the wall facing the subject. By positioning their head the laser will be aligned with a target on the wall, standardizing the head position at each time point. Additional details and procedures regarding the Quantificare system are available in **Attachments H.**

5. Treatment of Subjects and Follow-up

This study involves one treatment to be conducted at the treatment visit after obtaining informed consent, screening for inclusion/exclusion, complying with standardized photography requirements, completing a pregnancy test, if applicable, and completing randomization.

5.1 Study Treatment

5.1.1 Transducers

Two types of the Standard transducers with Energy Level 2 (EL2) will be used during this trial:

1. 4 MHz with a 4.5mm focal depth
2. 7 MHz with a 3.0mm focal depth

Two types of the Simulines transducers with EL2 will also be used:

1. 4MHz with a 4.5mm focal depth
2. 4MHz with a 3.0mm focal depth.

The region to be treated and the transducer used must be appropriately selected on the Ulthera® system and thus recorded on the Treatment Parameter System Record. The Ulthera system will default to EL2 with the study sites instructed not to adjust the energy level.

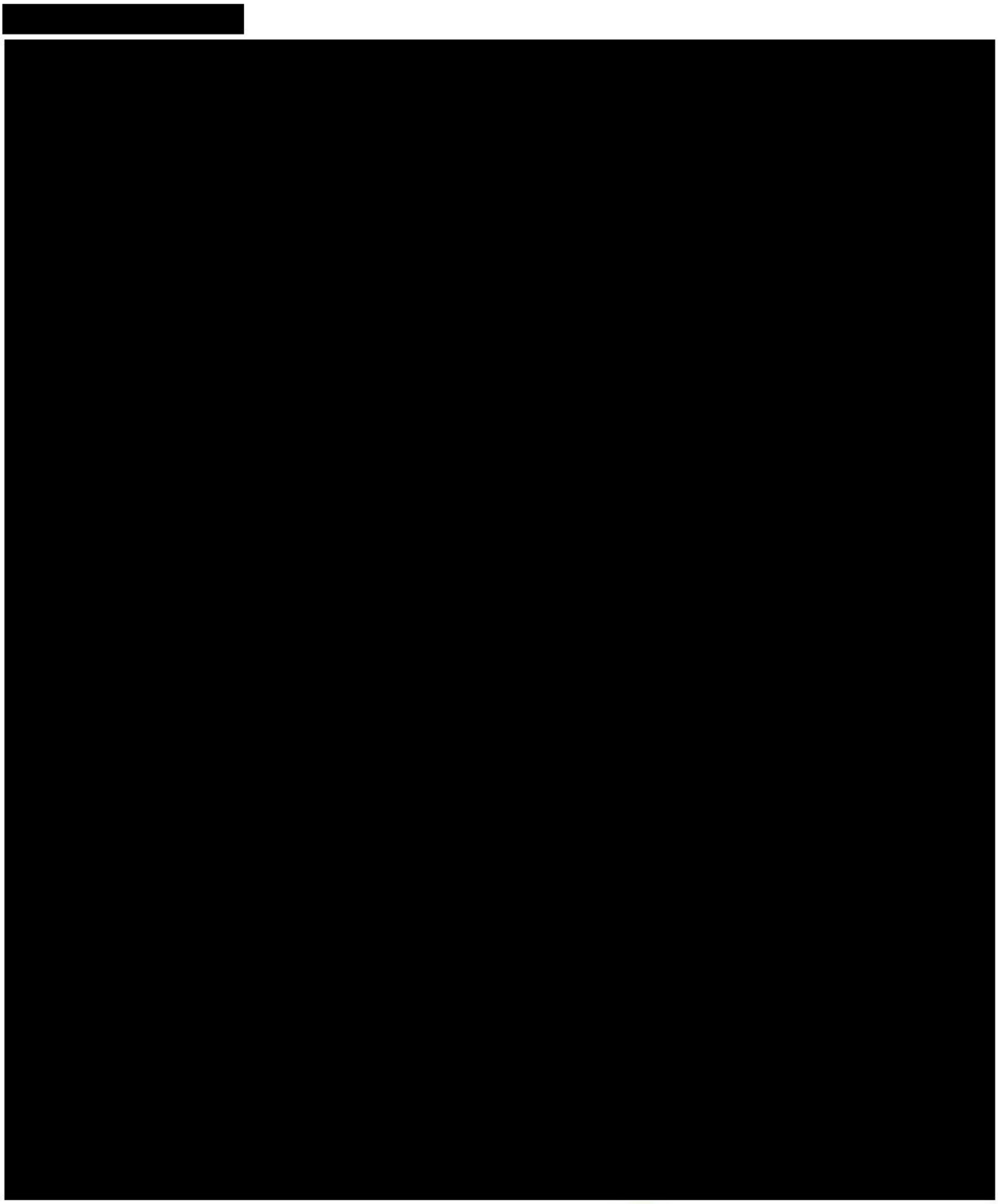
5.1.2 Pre-Treatment Medications

For this protocol, pre-treatment medications will be restricted to Ibuprofen (800mg) taken by all subjects at least 60 minutes but not more than two hours prior to study treatment.

5.1.3 Subject Preparation for Treatment

The investigator, sub-investigator, or qualified study staff member will first mark the skin areas to which an Ulthera® treatment is to be performed **(Figure 5.1.3-1)**. Treatment schematic is for illustrative purposes only. Treatment records for all regions will be maintained in accordance with this protocol.

[redacted]



5.1.4 Treatment

All study treatments will be performed by the investigator, sub-investigator, or qualified study staff member (i.e., study treatment clinician as designated by the principal investigator.) The study clinician performing efficacy assessments should remain blinded to the assigned treatment group, and therefore may not perform study treatments.

Ultrasound gel will be applied to the transducer, which will then be placed on the targeted skin surface, and ultrasound image will be obtained. Each area of the proposed treatment will be imaged first with the ultrasound device to ensure coupling between the transducer and skin. During the treatment procedure, the study treatment clinician will place multiple Ultherapy® treatment lines close to each other in the selected area, with each treatment line requiring about 3 seconds. When using the Simulines transducer the distance the transducer should be advanced between delivery of treatment lines should be doubled as 2 lines of treatment are laid down simultaneously. It is also recommended that at least 2 to 3 passes are used to deliver all lines in each section to allow for tissue cooling between passes of energy delivery. Treatment lines can be a maximum length of 25mm and will produce a series of thermal coagulative points.

Treatment lines to the area highlighted in **(Figure 5.1.3-1)** above will be administered as specified by Treatment Group. Energy joules delivered for study treatments will be 0.9J joules [EL2] for the Standard 4-4.5mm transducer and 0.30J [EL2] for the Standard 7-3.0mm transducer. [redacted]

All study treatments will begin with the 4.5mm depth. The entire 4.5mm depth treatment will be completed prior to continuing to the 3.0mm depth treatment. Treatment will be delivered in a lined pattern. The subject will be monitored during the treatment.

The time each treatment begins and ends will be captured and recorded on the source documents.

5.1.5 Acute Responses

For all exposures, acute responses (e.g., erythema or edema) will be observed by the study treatment clinician and photographically recorded within 30-60 minutes after exposure. If any Serious Adverse Events are noted, an AE Form should be completed.

5.1.6 Post-Treatment Sunscreen

Subjects will apply study-supplied sunscreen daily until Study Exit to help limit sun exposure.

5.2 Safety Variables

Prior to treatment, the subject's medical history will be reviewed, a urine pregnancy test will be performed (if applicable), and a physical examination will be conducted. During Ultherapy® treatment, the subject's pain levels will be monitored using a validated Numeric Rating Scale **(Attachment D)**. Average pain scores should be obtained following each region treated and for each transducer used during treatment. The average pain score for the entire region treated by each transducer will be recorded. A script will be used for collecting pain scores.

At each subsequent visit, the subject will be queried about adverse events and changes in concomitant medications, and the treatment area will be visually examined. A second pregnancy screening test will be performed at the 365-day follow-up visit.

5.3 Quantitative Measures

Submandibular/Submentum quantitative measurements calculated as detailed in **Attachment A**, comparing subjects treated using Simulines versus Standard transducers, will be obtained based on 2D study images obtained at follow-up visits post-treatment compared to baseline.

Comparison of improvement data for overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs obtained at follow-up visits post-treatment compared to baseline as detailed in **Attachment F.**

Secondary effectiveness will be assessed at baseline and 90 days using the validated, Merz Jawline Grading Scale (MJGS) **(Attachment G)** by independent, masked evaluators using photographs obtained at baseline and the 90-day follow-up visit. The evaluators will be trained and qualified on the MJGS by the sponsor and will remain masked throughout the study. The MJGS is an ordinal scale and ratings will be made based on a "snap-shot" at a single point in time and therefore will not be based on a comparison to a pre-treatment photograph.

The Global Aesthetic Improvement Scale (GAIS) **(Attachments B and C)** will be obtained at all post-treatment time points. The GAIS is a 5-point scale that rates global aesthetic improvement from the pre-treatment appearance. The ratings are worse, no change, improved, much improved, and very much improved. It was validated by Dr. Carutthers, et al. for this use. In this study, both live observation and photo review are utilized by the clinician (CGAIS) and subject (SGAIS) in order to assign a score. The CGAIS must be performed by the primary investigator, or a qualified study staff member delegated by the PI. Both the CGAIS and SGAIS should be completed in two steps:

- Based on a live assessment of the subject while referring to the subject's pre-treatment photographs (subjects should be given a hand mirror for this assessment); and
- Based on a comparison of the subject's pre-treatment photographs to the current post-treatment photographs.

A validated Numeric Rating Scale (0-10) **(Attachment D)** will be used to record subjects' pain scores during study treatment. Scores will be obtained for each region treated and for each transducer used.

A Patient Satisfaction Questionnaire (PSQ) **(Attachment E)** will be completed at the 90-day follow-up visit. The subject should complete this assessment while referring to baseline photos and using a hand mirror as well as comparing baseline and follow-up photographs.

The time to complete the study treatment for each group will be captured as treatment start time (time treatment started on the Ulthera System) and stop time (time treatment is ended on the Ulthera System) automatically recorded on the system treatment logs. The treatment logs are the source documents that are referred to when recording treatment times on the case report forms.

Volumetric changes from baseline compared to 90, 180, and 365 days post-treatment will be assessed using Quantificare 3D imaging as a secondary outcome measure at up to 3 sites. Please see **Attachment J.**

5.3.1 Primary Endpoint

Efficacy will be assessed based on quantitative measurements of neck and submental lift at 90 days post-treatment compared to baseline. Subject response is defined as ≥20 mm^2 reduction in 2D submental area from baseline.

(Note: this is the same methodology and success criteria which supported the FDA clearance of the submental/neck lift indication for this device). Simulines transducers will be considered non-inferior to Standard transducers using a non-inferiority margin of 15% between the two study arms. The study was powered based on the expected response rate of 73% as seen in the pivotal trial supporting the neck/submental lift indication FDA clearance K121700. The observed response rate of the prior pivotal trial (73%) was higher than the minimum response rate required (65%) for success of the supporting trial.

5.3.2 Secondary Endpoints

The secondary endpoints of this clinical trial include:

1. Subject response as measured by quantitative improvement measurements of submandibular and submental lift at 180 and 365 days post-treatment compared to baseline.
2. Comparison of improvement in overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs at 90, 180 and 365 days post-treatment compared to baseline.
3. Assessment of mean change from baseline to 90 days post treatment on the validated, Merz Jawline Grading Scale (MJGS) by independent masked evaluators.
4. Quantificare 3D imaging of up to 135 study subjects to assess volumetric changes from baseline compared to 90, 180, and 365 days post-treatment.
5. Patient satisfaction and patient reported improvement at 90 days post-treatment.
6. Comparison of average treatment times using Simulines transducers compared to average treatment times using Standard transducers.
7. Comparison of average pain scores using a validated Numeric Rating Scale to assess subjects' treatment-related comfort level with Simulines transducers versus Standard transducers.
8. Subject Global Aesthetic Improvement Scale (SGAIS) results assessing overall aesthetic improvement at 90, 180 and 365 days post-treatment.
9. Clinician Global Aesthetic Improvement Scale (CGAIS) results assessing overall aesthetic improvement at 90, 180, and 365 days post-treatment.

5.4 Blinding Assessment

Subjects and the study clinician performing efficacy assessments will remain blinded to the assigned treatment group for the duration of the study. Blinding will be assessed through completion of blinding questionnaires completed by both the subject and the blinded clinician at study end.

5.5 Follow-up

Subjects will be asked to return to the clinic for follow-up visits at 90, 180 and 365 days post-treatment.

At all visits, subjects will be assessed for safety and efficacy, standardized images will be taken (refer to Ulthera's study specific photography guidelines and procedures document), adverse events and protocol deviations will be assessed.

At the 90-day follow-up appointment in addition to the above referenced assessments, the subject will complete a Patient Satisfaction Questionnaire. An additional pregnancy test, if applicable, will be completed at the 365-day follow up visit.

5.6 Protocol Deviations

This study should be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of a subject requires a protocol deviation, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). If the deviation from the protocol is necessary to protect the physical well-being of a subject in an emergency, such protocol deviations must be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than five working days after the emergency occurred.

Any occurrence of pregnancy during the course of the trial must be reported to the Sponsor and documented as a protocol deviation.

In the event of a significant deviation from the protocol due to an accident or mistake, the investigator or designee must contact the Sponsor at the earliest possible time by telephone to discuss the deviation and its impact on the study and subject continuation in the study. These discussions will be documented by the investigator and the Sponsor, and reviewed by the monitor.

5.7 Withdrawal Criteria and Procedures

All subjects have the right to withdraw at any point during the study without prejudice. The investigator can discontinue any subject, at any time, if medically necessary. The reason for subject's withdrawal should be documented on the appropriate study-specific data form. The subject must undergo the recommended follow-up assessments specified for the last study visit unless contraindicated due to a medical condition. Withdrawn subjects will not be replaced.

5.8 End of Study (Completion)

All subjects who have signed an Informed Consent Form, except for screen failures, will be considered enrolled in the study. Subjects who complete the study duration will be considered to have completed the study. Any subject who does not return for a scheduled follow-up visit will be contacted at least twice by telephone to determine the cause for the missed visit and to try to get the subject scheduled for the follow-up. A new visit will be scheduled as soon as possible. All subjects should be followed until completing the study follow-up or until study discontinuation (withdrawal) for other reasons. The reason for study discontinuation should be documented for each subject. Subjects will be deemed "Lost-to-Follow-up" if they have not returned within six weeks after the last follow-up target. For any subject lost to follow-up at least three attempts to contact the subject must be documented; the attempts must be two phone calls/emails and a registered letter.

6. Statistical Analysis

6.1 Study Objective

The objective of this study is to demonstrate that the safety and efficacy of Simulines transducers at Energy Level 2 [EL2] is not inferior to treatment with Standard transducers at Energy Level 2 [EL2] in order to limit the energy level of both types of transducers to a maximum of EL2 for lift indications. To fulfill this objective we will be using the same treatment depths and regions treated as those used in the pivotal study that supported the submental/ neck clearance, but at EL2 instead of Energy Level 4 [EL4]. Simulines transducers deliver 2 lines of treatment per pulse (push of the button) versus Standard transducers which deliver 1 line of treatment per pulse.

6.2 Determination of Sample Size and Study Success

A sample size of 260 randomized subjects will be required to account for up to 16% attrition to have 80% power to determine non-inferiority given a response rate of 73% in both randomized groups and a non-inferiority margin of 15%. Response is defined as greater than 20 mm^2 reduction in neck and submental area from baseline. The study was powered based on the expected response rate of 73% as seen in the pivotal trial supporting the neck/submental lift indication FDA clearance K121700. The observed response rate of the prior pivotal trial (73%) was higher than the minimum response rate required (65%) for success of the supporting trial. Study success will be achieved given a statistically significant determination for non-inferiority for the primary efficacy objective. Statistical significance is determined using a one-sided α=0.05.

6.3 Analysis Populations

The intent-to-treat population is defined as all subjects who were randomized with study group defined by the randomization.

The per-protocol population is defined as the subset of ITT subjects who:

- met the major inclusion and exclusion criteria
- received within +/- 5% of the total lines per protocol for the randomized treatment
- had in-office follow-up visits either in window or out of window but within 7 days of window open/close
- had primary endpoint data available with acceptable photographic quality as determined by the 3rd party evaluator
- did not have any major protocol violations

The major inclusion/exclusion criteria include age 30 to 70 years, inclusion #3, #4, #8, adherence to photography procedures (i.e., removal of jewelry and makeup), exclusion #1, #7, #8, #11 - #15, #19, #21, #24, #27-#29.

The major protocol violations are defined as:

- use of any other pre-medication for pain besides ibuprofen and administration of ibuprofen less than 45 minutes or more than 135 minutes prior to initiation of study treatment
- any change to the energy level of the device during treatment
- accidental unblinding of investigators completing blinded assessments or subjects during treatment

6.4 General Statistical Analysis Methods

Descriptive statistics for each variable will be calculated which will include measures of central tendency, variation, a frequency histogram and a count of the number of missing values.

When the arithmetic mean is found not to be an appropriate measure of central tendency, alternative statistics will be considered (e.g. median). When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches or data transformations may be implemented. If data transformations are used they will be specified in the final clinical report.

6.4.1 Assessment of comparability of randomized groups and poolability of investigational sites

Summary tables describing the study population will be produced using subjects in the intent-to-treat population by randomized group. The study population will be described in terms of subject disposition, baseline characteristics, and concomitant medications. Subject disposition parameters will include number of subjects enrolled, treated, discontinued, and reasons for discontinuation. Baseline characteristics will include demographics, height, weight, BMI, and medical history.

The primary efficacy endpoint will be summarized by randomized group and investigational site in the observed intent-to-treat subjects. Although enrollment is set at a minimum of 20 subjects per site, if there is some unforeseen event preventing this minimum level of enrollment per site, investigational sites with fewer than 10 subjects will be combined for this purpose. A random center effect and a random center by randomized group (ITT) interaction will be included in the primary statistical model using logistic regression. If the p-value for the interaction term variance component is < 0.15, the interaction term and the random center effect will be retained in the model and the effect of treatment will be estimated using this model as an additional analysis to the primary objective. If the p-value for the interaction term variance component ≥ 0.15 and the random center effect is < 0.05, the random center effect alone will be retained in the model and the effect of treatment will be estimated using this model as an additional analysis to the primary objective. If neither is significant, the effect of treatment will not need to be re-estimated using a model that includes random center or center by treatment effects. The study is not powered to find a statistically significant treatment effect if significant center heterogeneity or effect modification is found, the models however, can be used to pool the data to assess the effect of center heterogeneity or effect modification on the estimated treatment effect.

6.4.2 Handling of Missing Data

A sensitivity analysis to the missing data for the intent-to-treat primary efficacy endpoint analysis will be conducted. The sensitivity analysis will include a best-case, worst-case and tipping point analysis. The best-case analysis will impute successes for the subjects with missing data randomized to test group and failures for the subjects with missing data randomized to the control group. The worst-case analysis will impute failures for subjects with missing data randomized to test group and successes for subjects with missing data randomized to control group. The tipping point analysis completes the primary efficacy endpoint analysis with each possible combination of missing data imputation between the best- and worst-case analysis. The goal of the tipping point analysis is to determine at what level of imputation the statistical evaluation of the endpoint loses statistical significance. If the worst-case analysis maintains statistical significance, the tipping point analysis is not necessary.

6.4.3 Efficacy Analysis

6.4.3.1 Primary Efficacy Analyses

Subjects included in the analysis: All ITT subjects will be included in the analysis.

Endpoint: Subject response is defined as ≥ 20 mm^2 reduction in 2D submental area from baseline. The left and right side value at baseline will be averaged to result in the 2D submental area at baseline. The left and right side value at 90 days will be averaged to result in the 2D submental area at 90 days. In the event, only either the left or right side data is available, it will be used. Response will be calculated as baseline – 90 days. The evaluator that determines 2D submental area is blinded to follow-up and study group.

Hypothesis:

H_o: The proportion of responders at 90 days as compared to baseline for the test group is inferior as compared to the control group given a non-inferiority margin of δ, $p_{control} - p_{test} \geq \delta = 15\%$.

H_a: The proportion of responders at 90 days as compared to baseline for the test group is not inferior as compared to the control group given a non-inferiority margin of δ, $p_{control} - p_{test} < \delta = 15\%$

Sample Size Rationale: The sample size calculation assumes 73% response in both randomized groups. Power was set at 80%, one-sided Type I error controlled at 5%, a non-inferiority margin of 15% and PASS 12 Non-inferiority for two independent proportions using the Z-test with unpooled variance was used. The sample size requires 109 subjects per randomized group to have data necessary to calculate the primary endpoint. The total sample size of 218 was corrected for up to 16% attrition to arrive at 260 subjects randomized in the study.

Primary Statistical Analysis: The primary statistical analysis will be conducted using the observed data in the intent-to-treat patients using the Z-test (unpooled) for two independent proportions. Statistical significance is determined using a one-sided α=0.05.

Additional Statistical Analysis: If there are intent to treat subjects with missing data, the analysis as specified in Section 6.4.1 Handling of Missing data will be conducted. The analysis in Section 6.4.1 regarding pooling will be conducted as specified in that section. The analysis will be completed for the subset of per protocol patients.

6.4.3.2 SECONDARY EFFICACY ANALYSES

The secondary efficacy analyses will be performed using subjects in the intent to treat population who have a non-missing assessment for the efficacy parameter at the time point being analyzed. The secondary endpoints are supportive in nature and are evaluated to provide additional information and are not intended to support additional claims. Descriptive statistics may be included in the labelling and for this purpose are defined as number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and number and proportion of observations for categorical variables. The secondary outcomes may additionally be completed for the subset of per protocol patients.

Secondary efficacy outcomes will be:

6.4.3.2.1 Quantitative improvement measurements of submandibular and submental lift at 180 and 365 days post-treatment compared to baseline.

Endpoint: Subject response is defined as ≥ 20 mm^2 reduction in 2D submental area from baseline. The left and right side value at baseline will be averaged to result in the 2D submental area at baseline. The left and right side value at 180 days will be averaged to result in the 2D submental area at 180 days. Similarly, at 365 days. In the event, only either the left or right side data is available, it will be used. Response will be calculated as baseline – follow-up. The evaluator that determines 2D submental area is blinded to follow-up and study group.

Statistical Analysis: A repeated measures model will be used to analyze the data from this objective. The dependent variable will be response (y/n). The independent variables will be study group and day of follow-up. A covariance structure will be used to account for the correlation expected among the repeated observations collected for each subject. The covariance structure that fits the data best, i.e. results in the lowest Schwarz Bayesian Information Criteria (BIC) value all else held constant will be used, among the

unstructured, compound symmetric or auto-regressive types. Statistical significance will be determined using a two-sided α=0.05.

6.4.3.2.2 Comparison of improvement in overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs at 90, 180 and 365 days post-treatment compared to baseline.

Endpoint: The proportion of "Improved, correct pre-post selection" out of the total number of responses. The total number of responses includes the number responding "Improved, correct pre-post selection", Improved, incorrect pre-post selection" and "No change".

Statistical Analysis: A repeated measures model will be used to analyze the data from this objective. The dependent variable will be the proportion meeting the endpoint. The independent variables will be study group and day of follow-up. A covariance structure will be used to account for the correlation expected among the repeated observations collected for each subject. The covariance structure that fits the data best, i.e. results in the lowest Schwarz Bayesian Information Criteria (BIC) value all else held constant will be used, among the unstructured, compound symmetric or auto-regressive types. Statistical significance will be determined using a two-sided α=0.05.

6.4.3.2.3 Assessment of mean change and ≥ 1 point improvement from baseline to 90 days post treatment on the validated, Merz Jawline Grading Scale (MJGS) by an independent masked evaluator.

Endpoints: Change in MJGS from baseline to 90 days and proportion of subjects with a ≥ 1 point improvement from baseline to 90 days post treatment. Three masked evaluators that will review subject photos and will be blinded to treatment assignment and follow-up.

Statistical analysis: The mean change in MJGS from baseline to 90 days will be compared between study groups using the Two-sample T-test. The proportion of subjects with ≥ 1 point improvement from baseline to 90 days post treatment will be compared using Fisher's exact test.

6.4.3.2.4 Quantificare 3D imaging of up to 135 study subjects to assess volumetric changes from baseline compared to 90, 180, and 365 days post-treatment.

Endpoints: Change in volume as calculated per the Quantificare 3D imaging system (see Appendix I) from baseline to 90, 180 and 365 days post-treatment. The evaluator that determines Quantificare volume is blinded to follow-up and study group.

Statistical Analysis: A repeated measures model will be used to analyze the data from this objective. The dependent variable will be change in volume. The independent variables will be study group and day of follow-up. A covariance structure will be used to account for the correlation expected among the repeated observations collected for each subject. The covariance structure that fits the data best, i.e. results in the lowest Schwarz Bayesian Information Criteria (BIC) value all else held constant will be used, among the unstructured, compound symmetric or auto-regressive types. Statistical significance will be determined using a two-sided α=0.05.

6.4.3.2.5 Patient satisfaction and patient reported improvement at 90 days post-treatment.

Endpoints: Patient reported satisfaction and patient reported improvement (see Appendix E) at 90 days post-treatment.

Statistical Analysis: The number and percent of respondents to each of the questions and categories will be summarized by study group.

6.4.3.2.6 Comparison of average treatment times using Simulines transducers compared to average treatment times using Standard transducers.

Endpoint: Treatment time as defined as the time treatment started and the time the treatment concluded as captured per the treatment log.
Statistical Analysis: Treatment time will be compared by study group using the Two-sample T-test.

6.4.3.2.7 Comparison of average pain scores using a validated Numeric Rating Scale to assess subjects' treatment-related comfort level with Simulines transducers versus Standard transducers.

Endpoint: Pain as measured using the validated numeric rating scale (Attachment D).

Statistical Analysis: A repeated measures model will be used to analyze the data from this objective. The dependent variable will be pain score. The independent variables will be study group, transducer depth (4.5 mm, 3.0 mm) and treatment location (cheeks, submandibular/submental). A covariance structure will be used to account for the correlation expected among the repeated observations collected for each subject. The covariance structure that fits the data best, i.e. results in the lowest Schwarz Bayesian Information Criteria (BIC) value all else held constant will be used, among the unstructured, compound symmetric or auto-regressive types. Statistical significance will be determined using a two-sided α=0.05.

6.4.3.2.8 Subject Global Aesthetic Improvement Scale (SGAIS) results assessing overall aesthetic improvement at 90, 180 and 365 days post-treatment.

Endpoint: SGAIS as measured at 90, 180 and 365 days post treatment.

Statistical Analysis: The number and percent observed in each category will be reported by randomized group for each follow-up. A repeated measures model will also be used to analyze the data from this objective. The dependent variable will be improved (y/n) with independent variables study follow-up and study group. A covariance structure will be used to account for the correlation expected among the repeated observations collected for each subject. The covariance structure that fits the data best, i.e. results in the lowest Schwarz Bayesian Information Criteria (BIC) value all else held constant will be used, among the unstructured, compound symmetric or auto-regressive types. Statistical significance will be determined using a two-sided α=0.05.

6.4.3.2.9 Clinician Global Aesthetic Improvement Scale (CGAIS) results assessing overall aesthetic improvement at 90, 180, and 365 days post-treatment.

Endpoint: CGAIS as measured at 90, 180 and 365 days post treatment.

Statistical Analysis: The number and percent observed in each category will be reported by randomized group for each follow-up. A repeated measures model will also be used to analyze the data from this objective. The dependent variable will be improved (y/n) with independent variables study follow-up and study group. A covariance structure will be used to account for the correlation expected among the repeated observations collected for each subject. The covariance structure that fits the data best, i.e. results in the lowest Schwarz Bayesian Information Criteria (BIC) value all else held constant will be used, among the unstructured, compound symmetric or auto-regressive types. Statistical significance will be determined using a two-sided α=0.05.

6.5 Safety Analyses

The safety analysis will be performed using subjects in the intent-to-treat population. The safety outcome will be incidence of all treatment-emergent adverse events, where "treatment-emergent" is defined as beginning or worsening after treatment initiation. Incidence of device-related adverse events will also be summarized separately.

7. Evaluation of Adverse Events

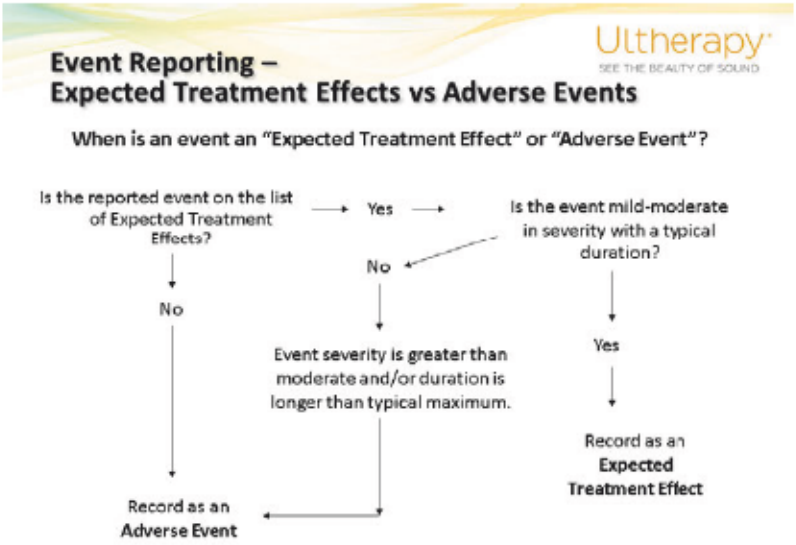
7.1 Definitions

An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered device-related by the investigator. During data analysis the Sponsor will evaluate all reported events and may re-categorize some events as expected treatment effects based on the following definition:

- Expected Treatment Effect: Any typical treatment side-effect of Ultherapy® of mild to moderate severity and lasting up to a typical maximum duration (see Figure 7.1.1 and Table 8.1.1).

All reported adverse events should be re-assessed by follow-up contact with the subject every 7 days until resolved.

FIGURE 7.1.1: EVENT REPORTING



7.2 Relationship to the Investigational Device

The investigator should assess the relationship of the adverse event to the investigational device. The relationship should be assessed using the categories presented in **Table 7.2-1.**

TABLE 7.2-1: RELATIONSHIP BETWEEN ADVERSE EVENTS AND INVESTIGATIONAL DEVICE

Definite	Definite relationship exists between the device and an adverse event
Probably Related	A reasonable causal relationship between treatment with the investigational device and an adverse event is more likely than not.
Possibly Related	A reasonable relationship exists between the device treatment and an adverse event, but the causal relationship is unclear or lacking.
Not Likely Related	A temporal relationship exists between the device treatment and an adverse event, but there is no reasonable causal relationship. For example the adverse event occurs in a time frame, which makes a causal relationship to device treatment improbable.
Unrelated	No relationship between treatment with the investigational device and the adverse event exists.

7.3 Unanticipated Adverse Device Effects (Events)

An unanticipated adverse device effect is defined as "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 supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

If an unanticipated adverse device effect occurs, the investigator should promptly notify the Sponsor of such an event, preferably within 48 hours of learning of the event. The investigator must promptly notify the reviewing IRB of such an event as soon as possible, but no later than 10 working days after learning of the event.

7.4 Serious Adverse Event

Each adverse event should be assessed for its seriousness. The definition below should be used for this assessment. Please note that the term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject. (Please refer to Section 7.6 for severity definitions.)

An adverse event should be classified as serious if it meets any of the following criteria:

a. Death
   Death was an outcome of the adverse event.
b. Life-threatening
   The subject was at substantial risk of dying at the time of the adverse event, or use or continued use of the device.
c. Hospitalization (initial or prolonged)
   Admission to the hospital or prolongation of hospitalization was a result of the adverse event.
d. Disability or Permanent Damage
   The adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change,

impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

e. Congenital Anomaly/Birth Defect
Exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Required Intervention to Prevent Permanent Impairment or Damage (Devices)
Medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

g. Other Serious (Important Medical Events)
The event does not fit the other outcomes, but the event may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

7.5 Reporting Requirements for Serious Adverse Events

Serious adverse events must be reported to the Sponsor as soon as possible, preferably within 24 hours but in no event later than 72 hours. The adverse event must be recorded on the subject's study-specific data form. The Sponsor will conduct an investigation. If the Sponsor determines that the investigation presents an unreasonable risk to subjects, all investigations or parts of the investigation presenting that risk will be terminated as soon as possible. The investigator must report serious adverse events to the reviewing IRB according to the IRB regulations at the study site.

7.6 Severity

Each adverse event should be assessed for its severity, or the intensity of an event experienced by the subject, using the following classifications:

1 = Mild	Discomfort noticed, but no disruption to daily activity
2 = Moderate	Discomfort sufficient to reduce or affect normal daily activity
3 = Severe	Inability to work or perform normal daily activity

7.7 Deaths

The investigator must notify the Sponsor as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of a subject's death, regardless of whether the death is related or unrelated to the investigational device. The investigator should attempt to determine, as conclusively as possible, whether the death is related to the device. The cause of death and the investigator's discussion regarding whether or not the death was device-related should be described in a written report. The investigator mush report death to the reviewing IRB according to the IRB regulations at the study site.

7.8 Pre-Existing Conditions

A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of the problem that has not been attributed to natural history.

8. Risk Analysis

8.1 Potential Risks

This treatment modality was designed to inherently minimize the risk to the subject. However, ultrasound exposure with subsequent heating of the soft tissue could involve the risks listed below:

TABLE 8.1.1: EXPECTED TREATMENT EFFECTS

Expected Treatment Effects	Duration
Bruising/Ecchymosis	Up to 2 weeks
Edema/Swelling	Up to 72 hours
Erythema/Redness	Up to 72 hours
Local Muscle Weakness/Paresis	Up to 6 weeks
Nodules	Up to 4 weeks
Acute Pain	Immediate/momentary (while energy is being delivered) - 2 hours
Skin Burn	Up to 4 weeks
Tenderness/Soreness/Pain/Sensitivity to Touch	Up to 2 weeks
Tingling/Paresthesia/Numbness/Nerve Related Transient Pain	Up to 6 weeks
Welting/Raised Areas of Edema	Up to 1 week

Common risks associated with Ibuprofen include nausea, diarrhea, dizziness, headaches and hypertension. NSAIDS (e.g., Ibuprofen) should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

These risks will be minimized or reduced by monitoring the subject during the treatment and observing the skin's response to receiving the treatment. If the treatment is not tolerated, the investigator must stop administering treatment for the subject's safety, and the subject will be followed for adverse events for 365 days.

Previous clinical studies with the Ulthera® System have shown that the sensory response was tolerable from the subject's and investigator's perspectives. The discomfort was transient and no subject had any residual pain beyond 30 minutes.

8.2 Minimization of Potential Risks

The risks listed above are minimized by performing two to three treatment line exposures and noting the subject's sensation and inflammatory response. Risks have also been minimized by prior testing (including preclinical, animal, and clinical) conducted with the Ulthera® System.

8.3 Potential Benefits

There is a potential benefit to participants of this study who are seeking lifting and tightening of skin laxity. Results of the study may contribute to further development of the ultrasound-based, non-invasive tissue-tightening procedure.

8.4 Justification for the Clinical Study

The current clinical study is justified based on the previous safe clinical experience with the Ulthera® System for cosmetic applications to facial skin, and the efficacy in related cosmetic applications for skin tightening. The current clinical plan is expected to result in lifting and tightening of the skin, wrinkle reduction, and achievement of a positive clinical outcome.

9. Device Management

9.1 Packaging

On a site-specific basis, the Ulthera® System will be shipped in a hard case designed to protect the system during delivery. Upon arrival at the clinical site, the Ulthera® System will be set up by Ulthera personnel for pre-study testing to ensure that the system is functioning properly.

9.2 Storage

Shipping and storage conditions include:

Shipping and Storage, System without Transducers

Shipping and Storage, with Transducers

9.3 Accountability

The investigator, or designee, must maintain an inventory record of study devices received, used for treatment, and returned to the Sponsor to ensure that the investigational device will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. There will be 100% accountability for all investigational Ulthera® Systems and transducers.

10. Regulatory and Ethical Requirements

This clinical study will be conducted in accordance with the Protection of Human Subjects Regulations, including Subpart B Informed Consent of Human Subjects (21 CFR Part 50); the Institutional Review Board Regulations (21 CFR Part 56); the Financial Disclosure by Clinical Investigators Regulations (21 CFR Part 54); and the Investigational Device Exemptions Regulations (21 CRF Part 812).

10.1 Informed Consent

Informed consent will be obtained from all subjects prior to study participation.

10.2 Institutional Review Board

Prior to initiation of any study procedures, the protocol, informed consent, and operators manual will be submitted to a duly constituted IRB for review and approval. In addition, any amendments to the protocol or Informed Consent Form will be reviewed and approved by the IRB. The Sponsor must receive a letter documenting IRB approval at the clinical site prior to the initiation of the study.

The investigator is responsible for providing the appropriate reports to its reviewing IRB during the course of the clinical study. These reports will include:

- Informing the IRB of the study progress periodically as required, but at least annually;
- Reporting any unanticipated adverse device effects within 10 working days of first learning of the event;
- Reporting any deviations from the clinical protocol to protect the life or well-being of a subject in the case of an emergency within five working days after the emergency occurred;
- Reporting the use of the device without obtaining informed consent from a subject within five working days of the event; and
- Providing any other reports requested by the IRB.

The IRB must be notified of study completion within 30 days of the final visit of the last subject and should be provided with a summary of the results of the study by the investigator.

10.3 Confidentiality of Subject Records

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or its representatives) will be allowed full access to inspect the records. All investigational devices and/or other materials collected will be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Subjects should be identified only by initials and unique subject numbers on study-specific data forms. If necessary, their full names may be made known to a regulatory agency or other authorized officials.

11. Reports and Records Management

This investigational study will comply with investigator reporting and record keeping requirements specified in 21 CFR Part 812. These requirements are summarized below.

11.1 Investigator Records

Prior to participation in the investigation, the investigator must provide the following documentation to the Sponsor:

- Investigator Agreement, signed by the investigator, which lists any physicians who will be involved in conducting the investigation under the direction of the primary investigator;
- A copy of the principal investigator's, sub-investigator's, other qualified study staff members' curriculum vitae;
- A letter signed by the chairperson of the IRB overseeing the conduct of this study indicating that the IRB has reviewed and approved this investigational plan; and

- A copy of the IRB-approved Informed Consent Form.

During the study, investigators are required to maintain on file the following accurate, complete, and current records relating to this study as described in 21 CFR §812.140. A summary of these records is listed below:

- All correspondence and required reports, which pertain to the study.
- Records of receipt, use, or disposition of study devices, including the type and quantity of devices; the dates of receipt; the serial numbers; the names of all persons who received, used or disposed of each device; and why and how many units of the device have been returned to the Sponsor, repaired, or otherwise disposed.
- Records of each subject's case history and exposure to the device.
- Signed and dated consent forms.
- Relevant observations, including records concerning adverse events, condition of each subject upon entering and results of diagnostic tests.
- Study-specific data forms and corrections to the forms.
- Protocol and amendments.
- Subject recruiting materials.
- Investigator curriculum vitae.

11.2 Investigator Reports

Investigators are required to prepare and submit to the Sponsor the following complete, accurate, and timely reports on this investigation when are required. These reports, which are listed below, are required by 21 CFR §812.150; additional reports may be requested by the Sponsor:

- The investigator will notify the Sponsor of a subject death occurring during the investigation, as soon as possible, preferably within 24 hours of learning of the subject's death, but in no event later than 48 hours. The investigator will notify the reviewing IRB of a subject death as specified by the IRB.
- The investigator will notify the Sponsor of any unanticipated adverse device effects within 48 hours after learning of the effect. The investigator will notify its reviewing IRB of any unanticipated adverse device effects, as soon as possible, but no later than 10 working days after learning of the effect.
- The investigator will notify the Sponsor of the withdrawal of IRB approval, as soon as possible, but no later than five working days after learning of the withdrawal.
- The investigator will provide current progress reports to the Sponsor and reviewing IRB at regular intervals and at least on an annual basis.
- The investigator will notify the Sponsor and reviewing IRB of any deviation from the investigational plan to protect the life and physical well-being of a subject in an emergency, as soon as possible, but no later than five working days after the emergency occurred.
- The investigator will notify the Sponsor and reviewing IRB that an informed consent was not obtained from a subject, as soon as possible, but no later than five working days after such an occurrence.
- The investigator will provide a final summary report to the Sponsor and reviewing IRB within three months after termination or completion of the study.
- The investigator will provide any other information upon the request of an IRB, FDA, or the Sponsor.

11.3 Data Collection

During each subject's visit to the clinic, an investigator participating in the study will record progress notes to document all significant observations. In addition, any contact with a subject by telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

For transmission to the Sponsor, information from the study progress notes and other source documents will be promptly transcribed to study-specific data forms, or study data may be recorded directly onto study-specific data forms. In this clinical trial, study-specific data forms may also serve as source documents. Transcription of study data onto study-specific data forms should be completed within 7 days of the study visit.

Any changes to information in the study progress notes, other source documents, and data forms will be initialed and dated in ink on the day the change is made by a site study staff member authorized to make the change. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

11.4 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, study-specific data forms, progress notes, electronic data, computer printouts, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons.

11.5 Records Retention at the Study Site

The investigator is responsible for retaining the necessary records, including a copy of the protocol, device labeling, study-specific data forms, medical records, original reports of test results, all study-related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

FDA regulations require all investigators participating in investigational device studies to maintain detailed clinical records during the investigation and for a period of at least two years after the latter of the following two dates:

1. The date on which the investigation is terminated or complete; or
2. The date the records are no longer required for purposes of supporting a premarket approval application.

The investigator must not dispose of any records relevant to this study without either:

1. Obtaining written permission from the Sponsor; or
2. Providing an opportunity for the Sponsor to collect such records.

The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA.

12. MONITORING PROCEDURES

12.1 MONITORING

The Sponsor has ethical, legal, and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the study), the Sponsor's monitors will visit the center during the study in addition to maintaining frequent telephone and written communication.

The following guidelines are provided to describe the Sponsor's procedures for monitoring the clinical studies, and meet the requirements specified in 21 CFR §812.46. If the investigator is not complying with the signed Investigator Agreement, the protocol, or any condition of the study (e.g., incomplete data forms), the Sponsor has the right to terminate the investigator's participation in the study.

The Sponsor is responsible for selecting study monitors qualified by training and experience to conduct monitoring of the trial, and for ensuring the quality of the study monitoring visits by the monitor.

The Sponsor's general monitoring procedures for investigational studies are described below.

12.2 PRE-STUDY MONITORING PROCEDURES

12.2.1 SELECTION OF MONITORS

There will be an overall study monitor, and additional monitors as needed, for the investigational study. The Sponsor determines the total number of monitors for its investigational studies based on the size and complexity of the study, the number and location of sites, the number of subjects, and the scope of the contractual obligations at each site. All monitors must be qualified by education, training, and experience.

12.2.2 CLINICAL INVESTIGATORS

Upon receipt of a signed Investigator Agreement and IRB approval letter, investigators will be sent the appropriate clinical study materials.

12.3 SITE INITIATION VISIT

A monitor will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations incurred in conducting a clinical study. The monitor or designated Ulthera representative will conduct an on-site site initiation visit where it will be ensured prior to study initiation that the investigator:

- Understands the requirements for a well-controlled study;
- Understands the clinical protocol;
- Understands his/her reporting obligations;
- Understands the requirements for device accountability;
- Understands and accepts the obligations to obtain informed consent in accordance with 21 CFR Parts 50 and 56;

- Understands and accepts the obligation to obtain IRB review and approval of the clinical investigation before it is initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56, and to keep the Sponsor informed of all IRB actions concerning the study;
- Understands and accepts the requirements regarding financial disclosure of clinical investigations, 21 CFR Part 54;
- Has adequate facilities and access to an adequate number of suitable subjects to conduct the investigation; and
- Has the required documentation on file, including IRB approval and a signed investigator agreement.

12.4 Periodic Monitoring Visits

Monitoring visits will be conducted in accordance with Guidance for Industry, Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2011. The monitor should visit each site at an appropriate frequency to ensure the following:

- Facilities continue to be adequate and acceptable.
- The protocol is being properly followed.
- The IRB has approved or been notified of any protocol changes.
- Accurate, complete, and current records are being maintained, and the information recorded and submitted to the Sponsor is representative of the subject's records and other supporting documentation.
- Accurate, complete, and timely adverse event reports are being submitted to the Sponsor.
- Informed consent has been obtained.
- The reason for a subject's withdrawal from the study has been documented.
- Reports are being submitted to the IRB and Sponsor.
- The appropriate staff is conducting study activities.

The investigator or designee must, upon request, provide to the Sponsor or FDA investigator the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, study-specific data forms and original documents and records such as clinic charts, subject informed consent forms, and treatment reports.

All study-specific data forms and other documentation related to the study will be reviewed upon receipt, and the site will be promptly notified of any deficiencies.

12.5 Frequency of Monitoring Visits

The frequency of monitoring visits will be determined on the basis of several factors, including:

- Duration of the study;
- Number of outstanding issues from previous visits;
- Number of subjects enrolled;
- Number of investigators/sites; and
- Complexity of the study.

Each site will undergo a monitoring visit on a regular basis.

12.6 Study Closure

All routine monitoring functions must be performed prior to the study closure visit; the study closure visit may be combined with a monitoring visit. The following tasks should be completed at the last visit by the monitor:

- Ensure that all forms and images have been sent to the Sponsor;
- Ensure that the Ulthera® System, study transducers, photographic equipment, and any other study supplies or equipment provided to the study site for study use have been returned to the Sponsor;
- Remind the investigator of the obligation to retain the records; and
- Prepare final monitoring report for Sponsor and IRB.

12.7 Reports of Monitoring Visits

Monitoring reports must be completed for all visits. Reports must include the following information:

- Date of the visit;
- List of study site personnel present; and
- A summary of the findings, problems, and actions taken to correct any deficiencies.

12.8 Additional Auditing

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

13. Confidentiality

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All investigational devices, subject bodily fluids, and/or other materials collected should be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Subject names and identifiers will be coded for privacy and subjects will be identified only by unique subject numbers on study-specific data forms. If necessary, their full names may be made known to a regulatory agency or other authorized officials.14. Amendment Policy

The investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB, except if the deviation from the protocol is necessary to protect the life and physical well-being of a subject in an emergency. Such protocol deviations must be reported to the Sponsor and the reviewing IRB as soon as possible, but no later than five working days after the emergency occurred.

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed by the investigator(s) and the Sponsor. If agreement is reached regarding the

need for an amendment, the Sponsor will write it. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for "administrative amendments", investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol; the scientific soundness of the investigational plan or protocol; and the right, safety or welfare of the human subjects involved in the investigation.

When, in judgment of the chairman of the IRB, the investigators and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written Informed Consent Form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before continued participation.

15. STUDY INVESTIGATORS

All investigators will be experienced with the cosmetic treatments using a variety of accepted clinical modalities.

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