Ultherapy

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CLINICAL PROTOCOL NUMBER ULT-302

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OPEN-LABEL, PROSPECTIVE EVALUATION OF THE ULTHERA® SYSTEM FOR LIFTING SUBMENTAL (UNDER THE CHIN) AND NECK TISSUE IN CHINESE SUBJECTS

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DATE: JANUARY 26, 2018

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Protocol Title:	Open-label, Prospective Evaluation of the Ulthera® System for Lifting Submental (Under the Chin) and Neck Tissue in Chinese Patients
Protocol Number:	ULT-302 / M960001052
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Senior Director, [redacted]

INVESTIGATOR SIGNATURE PAGE

Investigator Signature:

By signing this page, I agree to follow this Study Protocol and all applicable regulations.

Principal Investigator Signature	Date

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SPONSOR CONTACT INFORMATION

Protocol Title:	Open-label, Prospective Evaluation of the Ulthera® System for Lifting Submental (Under the Chin) and Neck Tissue in Chinese Patients
Protocol Number:	ULT-302 / M960001052
Sponsor:	Merz North America 6501 Six Forks Road Raleigh, NC 27615

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SPONSOR AGREEMENT

Merz North America (hereinafter "Study Sponsor") maintains responsibility for the ongoing safety of this clinical study 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 study 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. Within 6 months of study completion and final data analysis, Study Sponsor will provide the responsible IRB(s) with a copy of a final clinical study report.

INVESTIGATOR AGREEMENT AND CERTIFICATION

I hereby agree to participate in this clinical study 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 study 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
Co-/Sub-Investigator Name	

PROTOCOL SYNOPSIS

Company Name:	Ulthera, Inc.
Protocol Number:	ULT-302
Protocol Title:	Open-label, Prospective Evaluation of the Ulthera® System for Lifting Submental (Under the Chin) and Neck Tissue in Chinese Patients
Investigational Device:	Ulthera® System
Development Phase:	Pilot
Study Objective:	To evaluate the Ulthera® System for lifting submental (under the chin) and neck tissue in Chinese patients
Study Design:	Prospective, multi-site
Number of Subjects:	N = Up to 60 treated subjects (Up to 20 subjects in each of the three energy levels)
Study Treatment Groups:	Enrolled subjects will receive a dual depth Ultherapy® treatment using the 4-4.5mm and 7-3.0mm transducers. Treatments will be provided to the lower face, submental (under the chin) and neck area. Twenty enrolled subjects will be treated at each of three energy levels (EL2, EL3, and EL4).
Subject Population:	Adults between 35 and 65 years of age who meet the inclusion/exclusion criteria.
Inclusion Criteria:	1. Male or female, age 35 to 65 years. 2. Both parents of full Chinese decent. 3. Mild to moderate skin laxity of the submental (under the chin) and neck tissue as determined by the physician and trained assessors. 4. Adequate menton area to allow for quantitative analysis, as confirmed by photography images. 5. Willingness and ability to comply with protocol requirements, including returning for follow-up visit and abstaining from any other procedures in the areas to be treated through the follow-up period. 6. 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 with last menstrual bleeding at least 12 months prior to study; and b. Without a uterus and/or both ovaries. 7. Willing to take 600mg Ibuprofen as pre-treatment medication, at least 60 minutes but not more than two hours prior to study treatment. 8. Willingness and ability to provide written consent for study-required photography and adherence to photography procedures (i.e., removal of jewelry and makeup). 9. Willingness and ability to provide written informed consent 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. Presence of any hemorrhagic disorder or hemostatic dysfunction, herpes simplex, diabetes, epilepsy, bell's palsy or any physical or psychological condition that is deemed unacceptable by the investigator for participation in this study. 3. Severe solar elastosis.

4. Excessive subcutaneous fat in the area(s) to be treated.
5. Excessive skin laxity on the area(s) to be treated.
6. Significant scarring in the area(s) to be treated that would interfere with assessing results.
7. Open wounds or lesions in the area(s) to be treated.
8. Severe or cystic acne on the area(s) to be treated.
9. Active implants (e.g., pacemakers or defibrillators), or metallic implants in the treatment areas (dental implants not included.)
10. Inability to understand the protocol or to give informed consent.
11. Allergy or sensitivity to pre-treatment medication (ibuprofen).
12. Microdermabrasion, or prescription level glycolic acid treatment to the treatment area(s) within four weeks prior to study participation or during the study.
13. Marked asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin in the area(s) to be treated.
14. BMI greater than or equal to 30.
15. History of chronic drug or alcohol abuse.
16. More than 2-3 doses of any NSAID in any 2-week period prior to and throughout study.
17. History of autoimmune disease.
18. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study device.
19. Subjects who anticipate the need for inpatient surgery or overnight hospitalization during the study.
20. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
21. Concurrent enrollment or enrollment in any study involving the use of investigational devices or drugs within the past three months.
22. Current smoker as defined by
    a. Having smoked one or more cigarettes per day on a daily basis within the past year; or
    b. Smoke cessation within the past 6 months.
23. Current user of any nicotine-containing products, e.g., e-cigarettes, Nicorette gum, nicotine patches, etc.
24. History of the following cosmetic treatments in the area(s) to be treated:
    a. Skin tightening procedure within the past year;
    b. Injectable filler of any type within the past:
        i. 9 months for Hyaluronic acid fillers (e.g. Restylane)
        ii. 24 months for Ca Hydroxyapatite fillers (e.g. Radiesse)
        iii. 12 months for Long-lasting Hyaluronic acid (Juvéderm Voluma)
        iv. 24 months for Poly-L-Lactic acid fillers (e.g. Sculptra); and
        v. Ever for permanent fillers (e.g. Silicone, Artecoll)
    c. Neurotoxins within the past three months;
    d. Ablative resurfacing laser treatment;
    e. Nonablative, rejuvenative laser or light treatment within the past six months;
    f. Surgical dermabrasion or deep facial peels;
    g. Facelifts within the past year; or
    h. Any history of contour threads.
25. 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. Topical Retinoids within the past two weeks; c. Antiplatelet agents/Anticoagulants (Coumadin, Heparin, Plavix); d. 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 for Enrolled Efficacy Endpoint Subjects:	1. Screening Visit: a. Obtain informed consent b. Screen for inclusion/exclusion criteria; (obtain height and weight for BMI) c. Pregnancy screen (if applicable) d. Assess photography image for adequate menton area to allow for quantitative assessment e. Enrollment eligibility, based on degree of submental (under the chin) and neck tissue laxity (must be mild to moderate), will be determined by the physician and trained assessor's review and approval of screening images 2. Baseline / Treatment Visit (The screening visit may not be more than 14 days prior. Greater than 14 days between baseline/treatment visit and screening visit will require that the subject be re-screened to confirm enrollment eligibility.): a. Confirm eligibility for participation; b. Perform baseline photography using Vectra 3D photography system before treatment c. Complete subject lower face, submental (under the chin) and neck treatment 3. Post-treatment telephone contact a. 7±3 days – Capture adverse events 4. Follow-up Visits for efficacy evaluation: a. 90 ± 14 days i. Obtain Vectra 3D photography images (for quantitative measure and masked assessment); ii. Obtain height and weight for BMI iii. Obtain physician and subject global aesthetic improvement scores (GAIS); iv. Obtain subject satisfaction scores and v. Pregnancy screen (if applicable). 5. Visits for safety evaluation: a. Treatment Visit i. Pain assessment during treatment b. Immediately post-treatment i. Assess for adverse events. c. Day 7 Telephone Follow-up Visit i. Assess for adverse events d. Day 90 follow-up visit i. Assess for adverse events.
Primary Endpoint:	Assess improvement in overall lifting of submental (under the chin) and neck tissue as determined by a quantitative measure of tissue lift in the area using photographs taken with Mirror Photofile software and a Vectra 3D digital imaging system in each of the treatment groups 90 days post treatment in Chinese subjects.
Secondary Endpoints:	In each of the treatment groups, assess: 1. Improvement in overall lifting and tightening of skin as determined by subject

	response rate (improved, much improved or very much improved) on Physician Global Aesthetic Improvement Scale (PGAIS) as determined by live assessment at 90 days post-treatment compared to baseline photograph. 2. Improvement in overall lifting and tightening of skin as determined by subject response rate (improved or much improved) on Subject Global Aesthetic Improvement Scale (SGAIS) as determined by live assessment at 90 days post-treatment compared to baseline photograph. 3. Improvement in overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs at 90 days post-treatment compared to baseline. 4. Subject satisfaction and subject reported improvement at 90 days post-treatment.
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 [7]. Pain scores should be obtained following each region treated and for each transducer used during treatment. The patient reported average pain score for the entire region treated by each transducer will be recorded. In addition, the patient will be asked to provide an overall rating of their pain at the end of treatment. 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 90-day follow-up visit.
Statistical Analysis:	Descriptive statistics will be used to compare the submental lift, secondary endpoints and safety assessments between the 3 treatment groups at day 90 in this observational trial.
Study Hypothesis:	The hypothesis for this study is improvement in overall lifting and tightening of skin from baseline to 90 days post-treatment. For each treatment group (energy level), the measure of pre and Day 90 post treatment area of the chin and neck will determine the amount of tissue lift.
Study Duration:	**Estimated timeline: Up to 12 months**

STUDY OVERVIEW

Evaluation / Procedure	Screening Visit	Baseline / Treatment Visit	Day 7 ± 3 Telephone Follow-up	Day 90 ± 14 Follow-up
Informed Consent	√			
Eligibility Assessment (Inclusion/Exclusion[1])	√			
Demographics, Medical History, BMI	√			√[8]
Pregnancy Screening	√[6]			√
Investigator Skin Examination[2]	√	√		
Selection/Documentation of Treatment Plan[3]		√		
Treatment of Lower Face, Submental (under the chin) and Neck		√		
Subject Assessment of Pain[4]		√		
Vectra 3D Images		√[5]		√[9]
Quantitative Submental Lift Measure[7]		√		√
Masked Qualitative Assessments[7]		√		√
Patient Satisfaction Questionnaire				√
Aesthetic Improvement (Physician Global Aesthetics Improvement Scale - PGAIS)				√
Aesthetic Improvement (Subject Global Aesthetics Improvement Scale - SGAIS)				√
Adverse Event Assessment		*	*	*

*Complete AE Form when necessary.

1. Screening Form
2. Baseline Clinical Observations (Pre-Treatment) or Clinical Safety and Adverse Events (Post-Treatment and at Follow-up Intervals).
3. Treatment Parameters System Record
4. 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. Overall pain assessment will be completed following treatment completion.
5. Post-treatment images taken 30-60 minutes following Ultherapy® treatment.
6. Pregnancy:
    a. If a subject becomes pregnant after the Baseline visit and study treatment has been completed, the subject should continue to be followed.
    b. If a subject becomes pregnant after the Baseline visit but before any study treatments, the subject should be exited from the study.
7. Baseline and 90 day photos to be used after study completion to complete assessment.
8. Obtain BMI
9. Subjects may be asked to return to retake Day 90 image if photography issues are noticed following image assessment by photography consultant.

List of Acronyms and Definitions

Term	Definition
AE	Adverse Event
BMI	Body Mass Index
CV	Curriculum Vitae
FDA	Food and Drug Administration
EC	Ethics Committee
Elastosis	Degeneration of the elastic tissues
GAIS	Global Aesthetic Improvement Scale
GCPs	Good Clinical Practices
IRB	Institutional Review Board
MEEI	Massachusetts Eye and Ear Infirmary, Harvard Medical School
NRS	Numeric Rating Scale for pain assessment
PSQ	Patient Satisfaction Questionnaire
PGAIS	Clinician Global Aesthetic Improvement Scale
RF	Radiofrequency
Rhytidectomy	Mini-facelift
SAE	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
SMAS	Superficial Musculo-Aponeurotic System; terminal branches of sensory nerves of the face run in the layer above the Superficial Musculo-Aponeurotic System.
UCSD	University of California at San Diego
Ulthera® System	Ulthera® Ultrasound System and Accessories

CONTENTS

LIST OF FIGURES AND TABLES

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, lift lax submental (under the chin) and neck tissue, and improve lines and wrinkles of the décolleté.

The Ulthera System, in conjunction with the Ulthera DeepSEE transducer, allows for ultrasonic visualization of depths up to 8mm below the surface of the skin. The indicated use of the imaging is to visualize the dermal and subdermal layers of tissue to ensure proper coupling of the transducer to the skin and confirm appropriate depth of treatment such as to avoid bone.

The clinical study described in this protocol evaluates clinical outcomes associated with the non-invasive treatment to improve skin laxity and tightening. The Global Aesthetics Improvement Scale (GAIS) (**Attachment B and C**) to assess overall aesthetic improvement will be collected from both the study investigator and subject. Overall change will be measured at all study visits using Mirror Photofile software with a Vectra 3D digital imaging system. Subject satisfaction will be measured at protocol-specified visits using 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 a specific soft tissue layer under the superficial layers 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 (approximately $1mm^3$) micro-coagulation zones in the mid to deep reticular layer of dermis and sub-dermis, while sparing overlying papillary dermal and epidermal layers of skin. The device also incorporates an ultrasound imaging capability to evaluate the skin tissue.

1.4 Device Overview

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

1. Control unit with integrated touch screen;
2. Handpiece; and
3. One of six removable transducers.

FIGURE 1.4-1 PRIMARY COMPONENTS

Control Unit

Transducer **Handpiece**

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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. 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).

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 ultrasounds power and exposure duration. In general, higher frequencies are used for more superficial tissue effect compared to lower frequencies[5].

Six transducers are available. The transducers differ in the frequency of ultrasound energy emitted: 4 MHz (a high level of energy), 7 MHz (an intermediate level of energy), and 10 MHz (a low level of energy), as well as differing treatment depths (4.5mm, 3.0mm, or 1.5mm). 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	0.90J	4.5mm	0 to 8 mm
DS 7-3.0	7 MHz	0.30J	3.0mm	0 to 8 mm
DS 7-3.0*N*	7 MHz	0.30J	3.0mm	0 to 8 mm
DS 7-4.5	7 MHz	0.75J	4.5mm	0 to 8 mm
DS 10-1.5	10 MHz	0.18J	1.5mm	0 to 8 mm
DS 10-1.5*N*	10 MHz	0.18J	1.5mm	0 to 8 mm

Each treatment region is treated in a lined pattern delivering multiple lines of treatment. The transducer is advanced 2 to 3 mm within the region until all treatment lines have been delivered for that region and treatment of the region is complete. The user then moves to the next region of treatment. Treatment patterns under the current protocol are described in Section 5.1.

The Ulthera system has capability of 4 different energy levels to be used commercially. Transducer energy levels are shown in **Table 1.4-2**. This study will evaluate safety and efficacy of the 4-4.5mm and 7-3.0mm transducers at EL2, EL3, and EL4 in the Chinese population.

TABLE 1.4-2 TRANSDUCER ENERGY LEVELS

TRANSDUCER	ENERGY LEVELS [J]				
	LEVEL 0 (NO ENERGY)	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4
DS 4 - 4.5	0.00	0.75	0.90	1.00	1.20
DS 7-4.5	0.00	0.66	0.75	0.90	1.05
DS 7 - 3.0	0.00	0.25	0.30	0.35	0.45
DS 7 - 3.0N	0.00	0.25	0.30	0.35	0.45
DS 10-1.5	0.00	0.15	0.18	0.20	0.25
DS 10-1.5N	0.00	0.15	0.18	0.20	0.25

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 STUDY

1.6.1 CLINICAL SAFETY AND EFFECTIVENESS STUDY AT THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER (UTSW)

An open-label, prospective, non-randomized, clinical study 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 skin laxity.

2. Study Objective and Design

2.1 Study Objective

Assess improvement in overall lifting of submental (under the chin) and neck tissue as determined by a quantitative measure of tissue lift in the area using photographs taken with Mirror Photofile software and a Vectra 3D digital imaging system in each of the treatment groups in Chinese subjects.

2.2 Study Design

This study is an open-label, non-randomized clinical study to be conducted at up to seven clinical sites. Approximately 60 subjects (20 subjects per treatment group) who meet the eligibility criteria will be enrolled and treated with the Ulthera® System. Enrollment eligibility will be determined by the physician and trained assessors' review and approval of screening images.

Eligible subjects enrolled in the study will be treated using the Ulthera® System by the study investigator and/or trained clinician. Standardized images will be taken at screening, baseline (prior to treatment) and following treatment (30 to 60 minutes post-treatment) and at the 90-day post treatment visit using Mirror Photofile software and a Vectra 3D digital imaging system.

2.3 Duration of Study

Following the treatment visit, subjects will be followed for a total duration of up to 104 days.

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 / Treatment Visit	Day 7 ± 3 Follow-up	Day 90 ± 14 Follow-up
Informed Consent	√			
Eligibility Assessment (Inclusion/Exclusion[1])	√			
Demographics, Medical History, BMI	√			√[8]
Pregnancy Screening	√[6]			√
Investigator Skin Examination[2]	√	√		
Selection/Documentation of Treatment Plan[3]		√		
Treatment of Lower Face, Submental, and Neck		√		
Subject Assessment of Pain[4]		√		
Vectra 3D Images		√[5]		√[9]
Quantitative Submental Lift Measure[7]		√		√
Masked Qualitative Assessments[7]		√		√
Patient Satisfaction Questionnaire				√
Aesthetic Improvement (Physician Global Aesthetics Improvement Scale - PGAIS)				√
Aesthetic Improvement (Subject Global Aesthetics Improvement Scale - SGAIS)				√
Adverse Event Assessment		*	*	*

*Complete AE Form when necessary.

1. Screening Form
2. Baseline Clinical Observations (Pre-Treatment) or Clinical Safety and Adverse Events (Post-Treatment and at Follow-up Intervals).
3. Treatment Parameters System Record
4. 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. Overall pain assessment will be completed following treatment completion.
5. Post-treatment images taken 30-60 minutes following Ultherapy® treatment.
6. Pregnancy:
    a. If a subject becomes pregnant after the Baseline visit and study treatment has been completed, the subject should continue to be followed.
    b. If a subject becomes pregnant after the Baseline visit but before any study treatments, the subject should be exited from the study.
7. Baseline and 90 day photos to be used after study completion to complete assessment.
8. Obtain height and weight for BMI
9. Subjects may be asked to return to retake Day 90 image if photography issues are noticed following image assessment by photography consultant.

4. SUBJECT SELECTION AND PRE-TREATMENT

The study population will consist of healthy Chinese (both parents of full Chinese descent) males and females between 35 to 65 years of age with mild to moderate submental (under the chin) and neck tissue laxity and adequate menton area to allow for quantitative analysis, who have chosen to participate in this clinical study as evidenced by execution of the informed consent document. A physician assessor will confirm subjects eligibility based on submental (under the chin) and neck tissue laxity. Screening photos will be provided in a blinded manner so the trained assessor has no knowledge of what site is considering enrolling the patient.

4.1 PRE-TREATMENT RECRUITING/SCREENING

Subjects will be recruited from the study site's patient database and IRB approved advertisements. 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 (or legal representatives) before any study-related procedures, including any pre-treatment screening procedures, are performed. Investigators or delegated study personnel 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.

The IRB-approved Informed Consent Form will be signed by the study personnel obtaining consent. The subject will be given a copy of the signed Informed Consent Form. The investigative site will keep the original on file.

4.3 ELIGIBILITY

4.3.1 INCLUSION CRITERIA

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

1. Male or female, age 35 to 65 years.
2. Both parents of full Chinese descent.
3. Mild to moderate skin laxity of the submental (under the chin) and neck tissue as determined by physician and trained assessors.
4. Adequate menton area to allow for quantitative analysis, as confirmed by photography images.
5. Willingness and ability to comply with protocol requirements, including returning for follow-up visit and abstaining from any other procedures in the areas to be treated through the follow-up period.
6. 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 with last menstrual bleeding at least 12 months prior to study; and

   b. Without a uterus and/or both ovaries.
7. Willing to take 600mg Ibuprofen as pre-treatment medication at least 60 minutes but not more than two hours prior to study treatment.
8. Willingness and ability to provide written consent for study-required photography and adherence to photography procedures (i.e., removal of jewelry and makeup).
9. Willingness and ability to provide IRB approved written informed consent 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. Presence of any hemorrhagic disorder or hemostatic dysfunction, herpes simplex, diabetes, epilepsy, bell's palsy or any physical or psychological condition that is deemed unacceptable by the investigator for participation in this study.
3. Severe solar elastosis.
4. Excessive subcutaneous fat in the area(s) to be treated.
5. Excessive skin laxity on the area(s) to be treated.
6. Significant scarring in the area(s) to be treated that would interfere with assessing results.
7. Open wounds or lesions in the area(s) to be treated.
8. Severe or cystic acne on the area(s) to be treated.
9. Active implants (e.g., pacemakers or defibrillators), or metallic implants in the treatment areas (dental implants not included.)
10. Inability to understand the protocol or to give informed consent.
11. Allergy or sensitivity to pre-treatment medication (ibuprofen).
12. Microdermabrasion, or prescription level glycolic acid treatment to the treatment area(s) within four weeks prior to study participation or during the study.
13. Marked asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin in the area(s) to be treated.
14. BMI greater than or equal to 30.
15. History of chronic drug or alcohol abuse.
16. More than 2-3 does of any NSAID in any 2-week period prior to and throughout study.
17. History of autoimmune disease.
18. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study device.
19. Subjects who anticipate the need for inpatient surgery or overnight hospitalization during the study.
20. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
21. Concurrent enrollment or enrollment in any study involving the use of investigational devices or drugs within the past three months.
22. Current smoker as defined by:
    a. Having smoked one or more cigarettes per day on a daily basis within the past year; or
    b. Smoke cessation within the past 6 months.
23. Current user of any nicotine-containing products, e.g., e-cigarettes, Nicorette gum, nicotine patches, etc.
24. History of the following cosmetic treatments in the area(s) to be treated:
    a. Skin tightening procedure within the past year;

b. Injectable filler of any type within the past:
    i. 9 months for Hyaluronic acid fillers (e.g. Restylane)
    ii. 24 months for Ca Hydroxyapatite fillers (e.g. Radiesse)
    iii. 12 months for Long-lasting Hyaluronic acid (Juvéderm Voluma)
    iv. 24 months for Poly-L-Lactic acid fillers (e.g. Sculptra); and
    v. Ever for permanent fillers (e.g. Silicone, Artecoll)
c. Neurotoxins within the past three months;
d. Ablative resurfacing laser treatment;
e. Nonablative, rejuvenative laser or light treatment within the past six months;
f. Surgical dermabrasion or deep facial peels;
g. Facelifts within the past year; or
h. Any history of contour threads.

25. 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. Topical Retinoids within the past two weeks;
    c. Antiplatelet agents/Anticoagulants (Coumadin, Heparin, Plavix);
    d. 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.

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.

4.5 Subject Treatment Group Assignment

Subjects are not randomized in this study. All subjects will receive an Ultherapy ™ treatment at dual depth using the 4-4.5mm and 7-3.0mm transducers. Treatments will be provided to the lower face, submental (under the chin) and neck area. See Section 5.1 for Study Treatment details. Enrolled subjects will be assigned to one of 3 treatment groups:

Group EL2: Subjects will receive an Ultherapy ™ treatment at energy level 2 (EL2).

Group EL3: Subjects will receive an Ultherapy ™ treatment at energy level 3 (EL3).

Group EL4: Subjects will receive an Ultherapy ™ treatment at energy level 4 (EL4).

Twenty subjects will be enrolled in each group. Enrollment from the original protocol was in the following order: EL3, EL4 and EL2. This amendment (dated 26JAN2018) is to change the order of enrollment. Following amendment approval, approximately20 patients will be enrolled in EL2, EL3 and EL4 respectively. Enrollment will continue at an energy level until that treatment group is complete.

4.6 Study Images

The images in the study will be obtained using Mirror Photofile software and a 3D digital photography system for image collection, storage, and analysis. To ensure consistent, reproducible study photos from baseline photographs to the 90-day follow-up photographs, Study Sponsor's specific photography guidelines (refer to Photography Instruction Book for details) and procedures should be followed. The following photographs should be obtained at each specified study visit, for each imaging system used:

- Screening Vectra 3D photograph
- Baseline Vectra 3D photograph,
- Immediate (30-60 minutes) Post-treatment Vectra 3D photograph
- 90-Day Follow-up Vectra 3D photograph

Subject screening photos must be reviewed by trained assessor to ensure proper subject selection and enrollment eligibility and the subject's menton must be measured to ensure adequate area for quantitative assessment prior to study enrollment. The subject's baseline images are considered the pre-treatment comparator images.

5. Treatment of Subjects and Follow-up

In this study, subjects will receive a single Ultherapy treatment.

5.1 Study Treatment

5.1.1 Transducers

Two types of transducers will be used during this study:

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

Table 5.1-1

Transducer	GROUP EL2	GROUP EL3	GROUP EL4	Spacing (mm)	TCP's (#)	Depth (mm)	# of Lines
	Energy (J)						
DS 4-4.5	0.90	1.00	1	1	17	4.5mm	350
DS 7-3.0	0.30	0.35	0	1	23	3.0mm	310

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.

5.1.2 Pre-Treatment Medications

For this protocol, pre-treatment medication will be administered on-site and restricted to Ibuprofen (600mg) taken at least 60 minutes but not more than two hours prior to study treatment.

5.1.3 Subject Preparation for Treatment

The study investigator will first identify 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.

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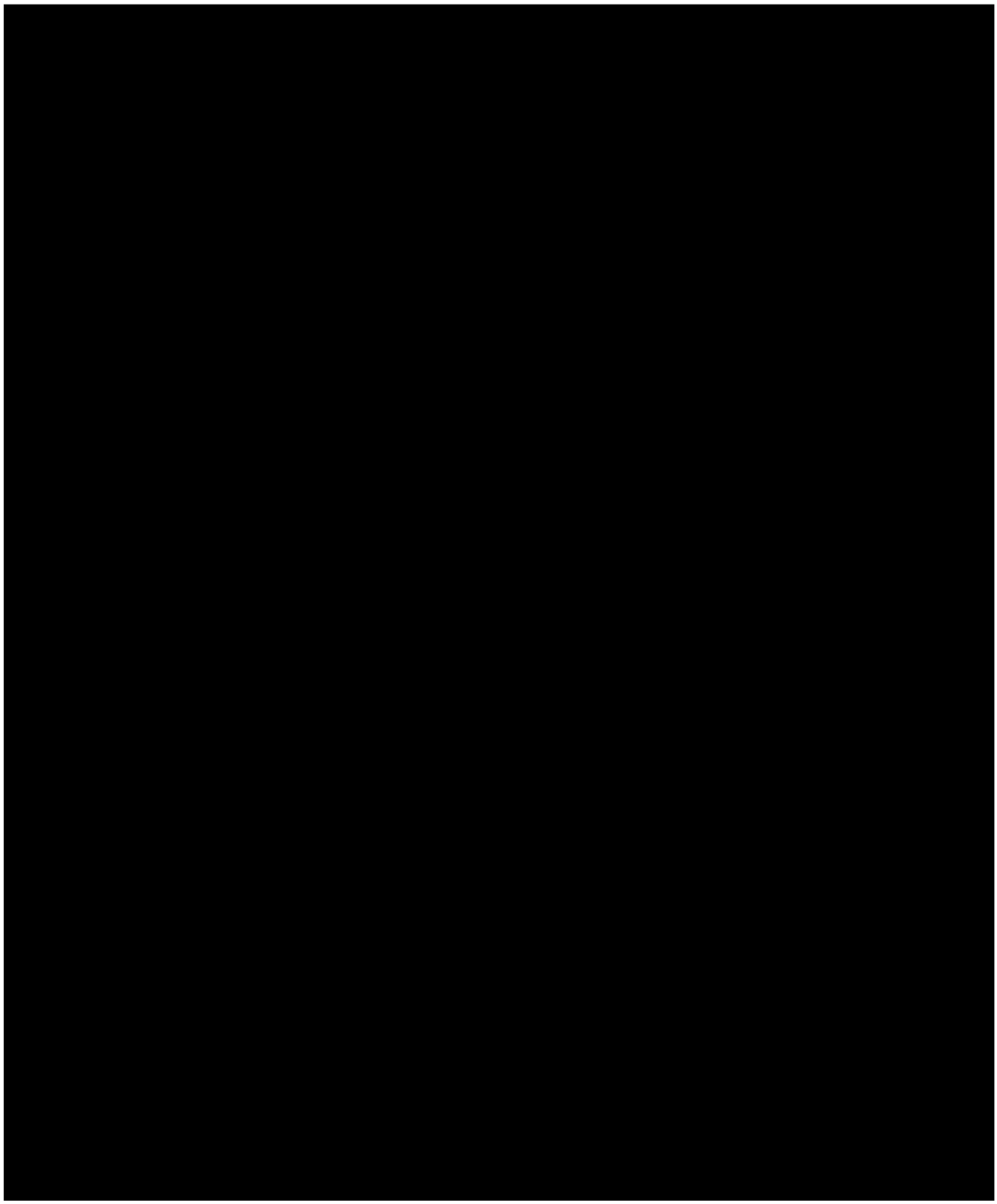
FIGURE 5.1.3-1 TARGET TREATMENT AREAS



5.1.4 TREATMENT

All study treatments will be performed by the study investigator and/or trained clinician.

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 (2 to 3mm) in the selected area, with each treatment line requiring about 3 seconds. Treatment lines can be a maximum length of 25mm and will produce a series of thermal coagulative zones.

Treatment lines to the area highlighted in (**Figure 5.1.3-1**) will be administered as specified by Treatment Group in Section 4.5. These energy settings should not be altered for any study treatments. The first transducer to be used in treatment is the 4-4.5mm, followed by the 7-3.0mm. 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.

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 (SAE) are noted, an SAE Form should be completed.

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 E**). 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. 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 90-day follow-up visit.

5.3 OUTCOME MEASURES

Quantitative submental lift measurements calculated as detailed in **Attachment A**, comparing improvement in overall lift, will be obtained based on Vectra 3D study images obtained at 90-day follow-up visit post-treatment compared to baseline. The quantitative scale used in the US Pivotal study was designed to measure a quantitative lift however; it was based on Caucasian anatomy. It measured the 2D submental/neck area using 5 quadrants from the menton/neck transition point back toward the neck. In Asian patients the distance from the menton/neck back towards the neck is not as long[6]. Therefore the 5th quadrant was dropped from the measure to account for this anatomical difference. This study will observe the amount quantitative lift by treatment group in this Chinese population.

The Global Aesthetic Improvement Scale (GAIS) (**Attachments B and C)** is a 5-point scale that rates global aesthetic improvement from the pretreatment appearance. The ratings are much worse, worse, no change, improved, and much improved. In this study both live observation and photo review are utilized by the physician (PGAIS) and subject (SGAIS) in order to assign a score. The PGAIS must be performed by the principal investigator. Both the PGAIS and SGAIS should be completed based on a live assessment of the subject while referring to the subject's

pre-treatment photographs on a sponsor-supplied electronic tablet (subjects should be given a hand mirror for assessment).

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**.

A validated Numeric Rating Scale (0-10) (**Attachment E**) will be used to record subject reported pain scores during study treatment and following treatment completion. Scores will be obtained for each region treated, for each transducer used, and for the overall treatment.

A Patient Satisfaction Questionnaire (PSQ) (**Attachment D**) will be completed at the 90-day follow-up visit. The subject should complete this assessment while referring to baseline photos on a sponsor-supplied electronic tablet and using a hand mirror.

5.3.1 Primary Endpoint

The primary endpoint is an assessment of the mean change (improvement) in overall lifting and tightening of skin in Chinese subjects at 90-days compared to baseline in each of the treatment groups as determined by a modified version of the validated quantitative measure of tissue lift in neck/submentum using photographs taken with Mirror Photofile software and a Vectra 3D digital imaging system.

5.3.2 Secondary Endpoints

The secondary endpoints of this clinical study include for each treatment group:

1. Improvement in overall lifting and tightening of skin as determined by subject response rate (improved or much improved) on Physician Global Aesthetic Improvement Scale (PGAIS) as determined by live assessment compared to baseline photograph.
2. Improvement in overall lifting and tightening of skin as determined by subject response rate (improved or much improved) on Subject Global Aesthetic Improvement Scale (SGAIS) as determined by live assessment compared to baseline photograph.
3. Improvement in overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs at 90 days post-treatment compared to baseline.
4. Subject satisfaction and subject reported improvement at 90 days post-treatment.

5.4 Follow-up

Subjects will be asked to return to the clinic for follow-up visits at 90 days post-treatment. At all visits, subjects will be assessed for safety and efficacy, standardized images will be taken (refer to study sponsor's study specific photography guidelines and procedures document), adverse events and protocol deviations will be assessed, and study outcome measures (GAIS, other study-specific assessments) will be completed.

At the 90-day follow-up appointment in addition to the above referenced assessments, the subject will complete a Patient Satisfaction Questionnaire and a pregnancy test, if applicable.

Subjects will be asked to return to the site for repeat image if 90-day follow-up image shows photography issues such as lighting inconsistencies, subject positioning, and/or shadowing as determined by photography consultant review.

5.5 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.

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.

5.6 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.

5.7 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 were treated and 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 two 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 Analyses

For primary and secondary endpoints, data will be summarized for each time point for which data for that parameter are available. Subjects with incomplete data will be included in summaries for which they have data available. Categorical variables will be summarized as frequencies and percentages in each category. Continuous and ordinal variables will be summarized as numbers of subjects, means, standard deviations, medians, and ranges. Graphical presentation of data will be provided, if deemed appropriate. All programs for data output and analyses will be written in SAS® version 9.4 or higher (SAS Institute, Inc., Cary, NC).

6.1 Efficacy Analysis

The primary analysis of efficacy will be based on the evaluable treated subjects, hence, only those subjects who received a complete or partial study treatment and completed the follow-up visit, and who have evaluable images

at baseline and 90-days post-treatment will be included in the analysis. No imputations will be performed for missing data.

The primary efficacy endpoint is the amount of improvement from baseline at 90 days after treatment. Descriptive statistics will compare mean values of improvement between the 3 treatment groups and 95% confidence intervals (CIs) will be calculated for each group. Additionally, the proportion of subjects achieving various levels of improvement may be calculated along with exact 95% CIs.

Any deviations from this statistical analysis plan will be documented with justification in the final report.

6.2 Secondary Analyses

The frequency and percentage for each of the following secondary endpoints will be reported for available data for the total population and by treatment group.

1. Improvement in overall lifting and tightening of skin as determined by subject response rate (improved, or much improved) on Physician Global Aesthetic Improvement Scale (PGAIS) as determined by live assessment at 90 days post-treatment compared to baseline photograph.
2. Improvement in overall lifting and tightening of skin as determined by subject response rate (improved, or much improved) on Subject Global Aesthetic Improvement Scale (SGAIS) as determined by live assessment at 90 days post-treatment compared to baseline photograph.
3. Improvement in overall lifting and tightening of skin as determined by a masked, qualitative assessment of photographs at 90 days post-treatment compared to baseline.
4. Subject satisfaction and subject reported improvement at 90 days post-treatment.

6.3 Safety Analyses

All adverse events (AE) and device related adverse events will be collected and reported during this study. AEs will be summarized overall, by seriousness and device relatedness including count. proportion of subjects experiencing each type of AE for all subjects and by treatment group will be provided.

Patient reported pain assessments collected throughout this study using the validated numeric scale will also be reported by treatment group and time point using descriptive statistics and include mean, standard deviation, median and range at minimum.

6.4 Interim Analyses

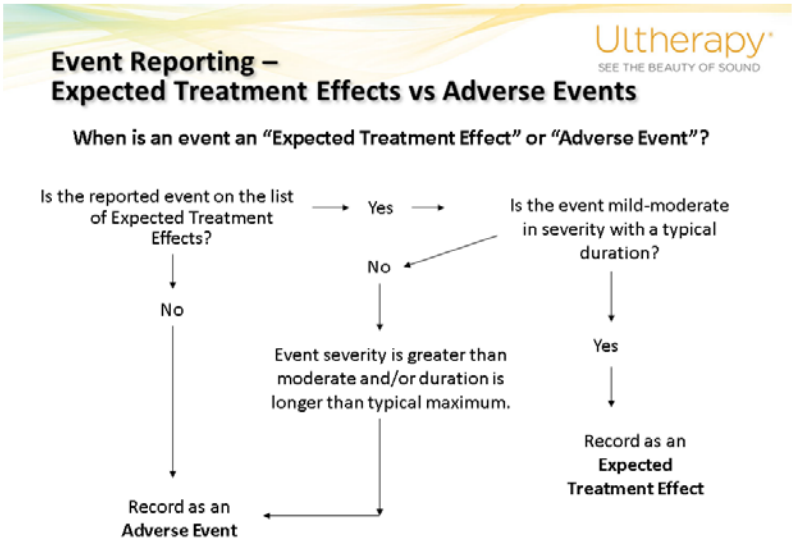
. If there is a need for an interim reporting of data, this will be outlined in the statistical analysis plan.

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. Reported events will be categorized as Expected Treatment Effects, i.e., any typical treatment side-effect of Ultherapy® of mild to moderate severity and lasting up to a typical maximum duration, or Adverse Events based on severity, duration and relationship to the Ulthera® device or Ultherapy® procedure/technique. See Figure 7.1.1.

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/procedure and an adverse event
Probably Related	A reasonable causal relationship between the device/procedure and an adverse event is more likely than not.
Possibly Related	A reasonable relationship exists between the device/procedure and an adverse event, but the causal relationship is unclear or lacking.
Not Likely Related	A temporal relationship exists between the device/procedure 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 device/procedure 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 notify the Sponsor as soon as possible of such an event. The investigator must promptly notify the reviewing EC 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 3 weeks
Edema/Swelling	Up to 2 weeks
Erythema/Redness	Up to 24 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 6 weeks
Tingling/Paresthesia/Numbness	Up to 6 weeks
Welting/Raised Areas of Edema	Up to 4 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 90 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 of submental (under the chin) and neck tissue laxity. Results of the study may contribute to further development of the ultrasound-based, non-invasive tissue-tightening procedure in Chinese patients.

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 and achievement of a positive clinical outcome in Chinese patients.

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

[redacted]

Shipping and Storage, with Transducers

[redacted]

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 view 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;
- Timely reporting any deviations from the clinical protocol to protect the life or well-being of a subject in the case of an emergency after the emergency occurred;
- Timely reporting the use of the device without obtaining informed consent from a subject;
- Providing any other reports requested by the IRB.

The IRB must be notified of study 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 "Medical Device Clinical Practice (GCP)", which FDA published. 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 and GCP office;
- A copy of the principal investigator's, sub-investigator's, other delegated study clinicians' 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 study, 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. The Ultherapy® treatment parameter system record will be considered the source document for the study treatment.

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 study, 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 EC approval letter, sites 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 2013, and the study-specific monitoring plan. 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, monitor 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 in compliance with the monitoring plan.

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.

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;
- A follow-up communication to the Principal investigator and study site outlining 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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Attachments: Outcome Measures

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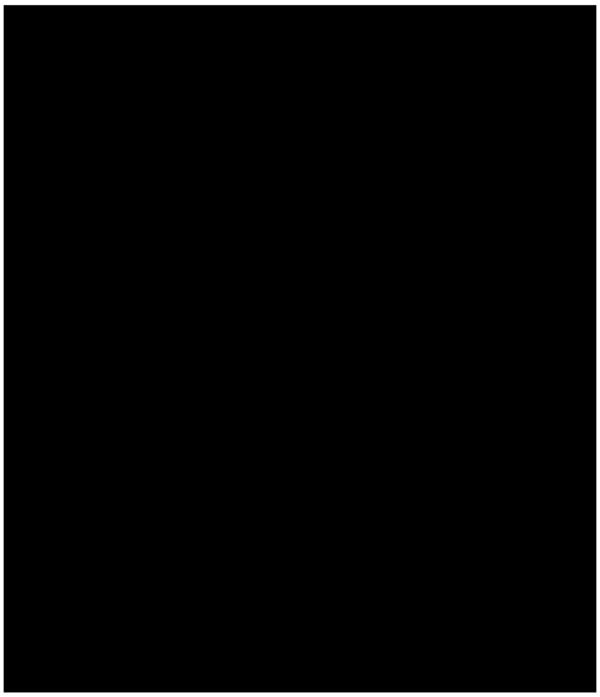

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