CLINICAL PROTOCOL NUMBER ULT-112

Evaluation of the Ulthera® System for Obtaining Lift and Tightening of the Cheek Tissue and Improvement in Jawline Definition and Submental Skin Laxity in Patients with Fitzpatrick Skin Phototypes 3 through 6

CONFIDENTIAL—PROPRIETARY INFORMATION

DATE: 2/15/2011
SIGNATURE PAGE

Company Name: Ulthera, Inc.
Address: 2150 S. Country Club Drive, Suite 21
         Mesa, Arizona 85210

Telephone: 480-619-4069 and 877-858-4372
Fax: 480-619-4071

Study Device: Ulthera® System

Protocol: Evaluation of the Ulthera® System for Obtaining Lift and
          Tightening of the Cheek Tissue and Improvement in Jawline
          Definition and Submental Skin Laxity in Patients with
          Fitzpatrick Skin Phototypes 3 through 6.

Draft Protocol Number: ULT-112
Draft Protocol Revision Date: 1/7/2011
Final Protocol Version Number: ULT-112
Final Protocol Version Date: 2/15/2011

Protocol Number ULT-112
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EVALUATION OF THE ULTHERA® SYSTEM FOR OBTAINING LIFT AND TIGHTENING OF THE CHEEK TISSUE AND IMPROVEMENT IN JAWLINE DEFINITION AND SUBMENTAL SKIN LAXITY IN PATIENTS WITH FITZPATRICK SKIN PHOTOTYPES 3 through 6

Protocol Number ULT-112

Development Phase: Pivotal clinical trial
Study Design: Prospective
Sponsor: Ulthera, Inc.
2150 S. Country Club Drive, Suite 21
Mesa, Arizona 85210
Clinical & Regulatory Affairs: Randall E. Miller, Ph.D.
Vice President, Clinical and Regulatory Affairs
Phone: 480-619-4069
Fax: 480-619-4071
Henry G. Hauser
Director of Clinical Affairs
Phone: 310-246-1303
Fax: 310-943-2335
Original Issue Date: 1/7/2011
Version: ULT-112
INVESTIGATOR AGREEMENT AND CERTIFICATION

I hereby agree to participate in this clinical study sponsored by Ulthera, Inc. (hereinafter “Study Sponsor”). I agree to conduct this investigation according to the requirements of the protocol provided by the Study Sponsor and in accordance with applicable regulations from the 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 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. 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.

I am aware that the Study Sponsor reserves the right to discontinue this investigation at any time.

My current curriculum vitae and the curriculum vitae of physicians at this institution who will participate as co-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 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:

[Signature]
Printed Investigator Name
## PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Company</th>
<th>Ulthera, Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational Device</td>
<td>Ulthera® System</td>
</tr>
<tr>
<td>Protocol Number</td>
<td>ULT-112</td>
</tr>
</tbody>
</table>

**Protocol Title:** Evaluation of the Ulthera® System for Obtaining Lift and Tightening of the Cheek Tissue and Improvement in Jawline Definition and Submental Skin Laxity in Patients with Fitzpatrick Skin Phototypes 3 through 6.

**Clinical Phase:** Pivotal Study

**Study Objectives:** To evaluate the Ulthera® System for obtaining lift and tightening the cheek tissue, and improving jawline definition and submental skin laxity in patients with Fitzpatrick skin phototypes 3 through 6.

**Study Design:** Prospective, non-randomized, clinical trial with masked evaluation

**Subject Population:** Adults between 30 and 65 years of age who have chosen an Ulthera Treatment, who provided informed consent, and who meet the inclusion/exclusion criteria.

**Inclusion Criteria:**

1. Male or female, aged 30 to 65 years.
2. Subject in good health.
3. Subjects who desire lift and tightening of cheek tissue, improvement in jawline definition and/or submental skin laxity
5. Understands and accepts the obligation not to undergo any other procedures in the areas to be treated through the follow-up period.
6. 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.
7. Subjects of childbearing potential must have a negative urine pregnancy test result at Visit 1 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) A bilateral tubal ligation at least six months prior to study enrollment.
8. Absence of physical conditions unacceptable to the investigator.
9. Willingness and ability to provide written consent for study-
required photography and adherence to photography procedures (i.e., removal of jewelry and makeup).

10. Willingness and ability to provide written informed consent and HIPAA authorization prior to performance of any study-related procedure.

Exclusion Criteria:

1. Pregnant, lactating, planning to become pregnant, or not using a reliable form of birth control.
2. Presence of an active systemic or local skin disease that may affect wound healing.
3. Severe solar elastosis.
4. Excessive subcutaneous fat on the cheek.
5. Excessive skin laxity on the lower face and neck.
6. Significant scarring in areas to be treated.
7. Significant open facial wounds or lesions.
8. Severe or cystic acne on the face.
9. Presence of a metal stent or implant in the facial area to be treated.
10. Inability to understand the protocol or to give informed consent.
11. Retinoid, microdermabrasion, or prescription level glycolic acid treatments to the intended treatment area within two weeks prior to study participation or during the study.
12. Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
13. History of chronic drug or alcohol abuse.
15. Concurrent therapy that, in the investigator’s opinion, would interfere with the evaluation of the safety or efficacy of the study device.
16. Subjects who anticipate the need for surgery or overnight hospitalization during the study.
17. Subjects who, in the investigator’s opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
18. Concurrent enrollment in any study involving the use of investigational devices or drugs.
19. Current smoker or history of smoking in the last five years.
20. History of the following cosmetic treatments in the facial area to be treated:
   a. Facial skin tightening procedure within the past year;
   b. Injectable filler of any type in the lower 2/3 of the face within the past year;
   c. Botulinum neurotoxin Type A in the lower facial area or neck (platysma) within the past six months;
   d. Ablative resurfacing laser treatment;
   e. Nonablative, rejuvenative laser or light treatment within the past six months;
   f. Dermabrasion or deep facial peels; or
   g. Facelifts, blepharoplasty, browlift, or contour threads.
21. History of using the following prescription medications:
   a. Isotretinoin or other oral, systemic retinoids within the past six months;
   b. Coumadin, Heparin, or antiplatelets; or
   c. Psychiatric drugs that in the investigators opinion would impair the subject from understanding the protocol requirements or understanding and signing informed consent

<table>
<thead>
<tr>
<th>Treatment Outline:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Initial visit: a) screen for inclusion/exclusion criteria; b) obtain informed consent; and c) if subject meets all criteria, perform baseline facial photography and the first treatment.</td>
</tr>
<tr>
<td>2. The primary efficacy endpoint of this clinical trial is improvement in overall lifting and tightening of skin as determined by qualitative assessment of photographs at three and six months post-treatment compared to baseline, based on a masked reviewer assessment.</td>
</tr>
<tr>
<td>3. Follow-up visits for efficacy evaluation: a) 90 ±7 days, 180 ±7 days (obtain images, GAIS scores from investigator) b) 90 ±7 days, 180 ±7 days (obtain GAIS scores from subject and patient satisfaction questionnaire)</td>
</tr>
<tr>
<td>4. Follow-up visits for safety evaluation: a) immediately post-treatment; b) 90 ±7 days; c)180 ±7 days.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Efficacy Endpoint:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in obtaining lift and tightening of the cheek tissue, jawline definition and submental skin laxity as determined by a masked, qualitative assessment of photographs at 90 and 180 days post-treatment compared to baseline.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Improvement in skin laxity will be measured at all visits using a digital imaging system.</td>
</tr>
<tr>
<td>2. The Principal Investigator and subject will complete a GAIS assessing overall aesthetic improvement at days 90, and 180 post treatment.</td>
</tr>
<tr>
<td>3. The subject will complete a patient satisfaction questionnaire at the 90-day and 180-day follow-up visit.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety Variables:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 site will be visually examined. Subject assessment of pain using a 10-point scale post treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Duration:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given two months for recruitment, the anticipated study duration is eight months.</td>
</tr>
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## STUDY OVERVIEW

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Case Report Form</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening and Initial Evaluation</td>
<td>Informed Consent</td>
<td>√</td>
<td>Day 90±7</td>
</tr>
<tr>
<td></td>
<td>Screening CRF (Includes inclusion/exclusion criteria, eligibility assessment, demographics and medical history, and clinician assessment)</td>
<td>√</td>
<td>Day 180±7</td>
</tr>
<tr>
<td>Efficacy Assessments</td>
<td>Photography for evaluating clinical improvement of face and neck</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Safety</td>
<td>Images for assessing edema/erythema of the face) and Adverse Event Forms</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Safety</td>
<td>Adverse Event Form</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Aesthetic Improvement</td>
<td>GAIS(^{(1)}) Form</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Patient Satisfaction</td>
<td>PSQ(^{(2)}) Form</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

**NOTES:**
(1) Global Aesthetic Improvement Scale (GAIS) Score
(2) Patient Satisfaction Questionnaire
# LIST OF ACRONYMS AND DEFINITIONS

<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event severity</td>
<td>The intensity of an adverse event, which can range from mild to moderate to severe. See Section 8.6 for more detail.</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CV</td>
<td>curriculum vitae</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>Elastosis</td>
<td>degeneration of the elastic tissues</td>
</tr>
<tr>
<td>GAIS</td>
<td>Global Aesthetic Improvement Scale</td>
</tr>
<tr>
<td>GCPs</td>
<td>Good Clinical Practices</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>MEEI</td>
<td>Massachusetts Eye and Ear Infirmary, Harvard Medical School</td>
</tr>
<tr>
<td>PSQ</td>
<td>patient satisfaction questionnaire</td>
</tr>
<tr>
<td>RF</td>
<td>radiofrequency</td>
</tr>
<tr>
<td>Rhytidectomy</td>
<td>mini-facelift</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>An adverse event that results in or contributes to death or is life threatening. See Section 8.4 for more detail.</td>
</tr>
<tr>
<td>SMAS</td>
<td>Superficial Musculo-Aponeurotic System; terminal branches of sensory nerves of the face run in the layer above the Superficial Musculo-Aponeurotic System</td>
</tr>
<tr>
<td>UCSD</td>
<td>University of California at San Diego</td>
</tr>
<tr>
<td>Ulthera® System</td>
<td>Ulthera® Ultrasound System and Accessories</td>
</tr>
</tbody>
</table>
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1. INTRODUCTION

1.1 Name and Indications for Use
The Ulthera® System 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 imaging skin and sub-dermal tissue.

The clinical trial described in this protocol evaluates clinical outcomes associated with the non-invasive treatment to improve skin laxity and tightening. The Global Aesthetic Improvement Scale (GAIS) assess overall aesthetic improvement. Overall volumetric change will be measured at all study visits using a standardized imaging system. Patient satisfaction will be measured at protocol-specified visits using a Patient Satisfaction Questionnaire.

1.2 Disease Background

Various energy delivery devices have been developed in an effort to treat facial rhytids. All of these devices, however, are used solely to treat the superficial layers of skin. For example, the CO$_2$ laser has been used extensively for facial resurfacing in the treatment of rhytids. Two mechanisms of action of the CO$_2$ laser are thought to contribute to its
resurfacing effects: (i) ablating and removing the most superficial layer of skin (epidermis); and (ii) delivering energy to the deeper dermis to create a lesion in the collagen. This lesion incites a “wound healing” response, in which fibroblasts synthesize and lay down new collagen. This collagen remodeling process is the crucial step in facial rejuvenation.

The CO₂ laser also has a dramatic “skin tightening effect,” caused by the heat-induced shrinkage of the collagen fibers and disruption of collagen cross-linking bonds. The thermal induced shrinkage of collagen occurs when connective tissue is heated to 65-75° C. However, heating beyond this narrow thermal range causes progressive denaturation of collagen, leading to complete destruction of collagen fibers and possible scar formation. Many other types of lasers (Smoothbeam, Cooltouch, etc.) have demonstrated a similar thermal induced skin tightening effect. Current wavelengths of these lasers limit the depth of energy delivered to the dermis. This limited penetration is unlikely to be overcome in the future scattering of laser light increases greatly as a function of penetration depth in tissue. Another limitation is that lasers deliver a conical light illumination tissue, proportionally delivering energy to the entire path of light penetrating into tissue and resulting in disruption of the epidermal tissue. Disruption of epidermal tissue typically results in crusting and peeling for approximately two weeks and the risks associated with loss of the protective epidermal barrier.

Although CO₂ laser resurfacing has been proven largely successful for the treatment of rhytids, the undesirable postoperative intense inflammatory response and its associated appearance have caused the demand for this procedure to drop dramatically. In an effort to minimize postoperative changes, physicians have attempted to develop various “Nonablative Skin Resurfacing” methods (e.g., Radiofrequency – Thermage) to induce collagen shrinkage and remodeling while preserving the epidermis. Ultrasound is an energy modality that can be focused to penetrate deeper in the tissue and cause thermal ablation to avoid the undesirable postoperative effects observed with CO₂ laser resurfacing the superficial layers. Ultrasound can also be used to image the region of interest. The Ulthera® System delivers ultrasound energy to cutaneous layers in the skin, such as the reticular dermis. Treatment with the Ulthera® System creates small focal lesions in the skin, causing thermally induced contraction of tissue, and a “wound-healing” response to stimulate the formation of new tissue and collagen remodeling. Focused ultrasound heating has several potential advantages over lasers and radiofrequency (RF) devices such as Thermage®. Focused ultrasound energy is able to confine heating to small focal regions with a combination of precision and depth not possible with lasers or RF devices. With a different transducer selection, the system can
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 a focal lesion 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 effect.

The device is designed and configured to produce small (approximately 1 mm³) micro-thermal lesions 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: 1) the control unit with integrated touch screen; 2) the handpiece; and 3) one of three removable transducers (Figure 1.4-1).

Figure 1.4-1. Main Components of the Ulthera® System: Control Unit, Handpiece, and Transducer

Use of the Ulthera® System is an automatic, computer-driven process that includes a planning stage prior to the treatment stage. The transducer can be used to image the treatment area prior to and during the treatment stage. The face and neck are divided into the following regions: upper third of face (hairline to cheekbone), lower third of face (cheekbone to jawline), and neck...
(submental, submandibular, and lower). During the planning phase, a treatment protocol is initiated by selecting the desired treatment region and the appropriate transducer is displayed.

Three transducers are available. The transducers differ in the frequency of ultrasound energy emitted: either 4 MHz (a higher level of energy) or 7 MHz (an intermediate level of energy) and treatment depth (either 3.0 or 4.5 mm). All transducers can image tissue up to 8 mm in depth. Transducer capabilities are shown in Table 1.4-1.

<table>
<thead>
<tr>
<th>Transducer Types</th>
<th>Treatment Frequency</th>
<th>Treatment Depth</th>
<th>Image Depth</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS 4 - 4.5</td>
<td>4 MHz</td>
<td>4.5 mm</td>
<td>0 to 8 mm</td>
</tr>
<tr>
<td>DS 7 - 3.0</td>
<td>7 MHz</td>
<td>3.0 mm</td>
<td>0 to 8 mm</td>
</tr>
<tr>
<td>DS 7 - 4.5</td>
<td>7 MHz</td>
<td>4.5 mm</td>
<td>0 to 8 mm</td>
</tr>
</tbody>
</table>

Each region of the face is treated in a lined pattern, with the maximum number of allowable lines indicated by the protocol. The therapy process is delivered in the lined pattern, with the transducer being advanced 2 to 3 mm along the line until the treatment line is complete. The user then moves to the next line of energy to complete treatment of the region. Treatment patterns under the current protocol are described in Section 5.4.

1.5 Preclinical Studies

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, well-confined thermal lesions 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 4.5 mm and 6 mm. The focal depths of the 7 MHz transducer were 3 mm and 4.5 mm. These studies further demonstrated...
1.6 Clinical Studies

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, or 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 all three 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 - 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 on the tissue excised from those subjects who underwent a delayed facelift (4 - 12 weeks following treatment with the Ulthera® System). No definitive findings of discrete coagulative changes were observed in the delayed...
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 procedure and 2) to 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 Ulthera 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 eyebrow height and characteristics by reviewing in a randomized order the Day-0 pre-treatment and Day-90 post-treatment 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 procedure. In addition, 75.7% of the subjects demonstrated a measurable improvement in eyebrow height at Day 90 post-treatment.
1.7 Study Purpose
The purpose of this prospective, single-treatment clinical trial is to evaluate the efficacy of the Ulthera® System for the non-invasive treatment of the face and neck in obtaining lift and tightening of the cheek tissue and improvement in jawline definition and submental skin laxity in patients with Fitzpatrick skin phototypes 3 through 6.

1.8 Study Duration
The follow-up period for this clinical trial is six months post-treatment. Subject recruitment will require approximately two months. Thus, the anticipated duration of the study is eight months.

2. STUDY RATIONALE AND OBJECTIVES

2.1 Study Rationale
The Ulthera® System has been demonstrated to be safe and effective for non-invasive dermatological treatment to produce eyebrow lift through tissue coagulation and tightening. The mechanism of action of the Ulthera® System is the creation of small focal lesions in the skin, causing thermally induced contraction of tissue and a "wound-healing" response to stimulate the formation of new tissue and to cause a skin-tightening effect from collagen remodeling. This effect would similarly be expected to produce an aesthetic improvement of the face and neck, particularly in lift and tightening of the cheek tissue, improvement in jawline definition and submental skin laxity in patients with Fitzpatrick skin phototypes 3 through 6.

2.2 Study Objectives
The primary objective of this study is to demonstrate aesthetic improvement of the face and neck, particularly in lift and tightening of the cheek tissue, improvement in jawline definition and submental skin laxity in patients with Fitzpatrick skin phototypes 3 through 6.

Additionally, patient satisfaction will be assessed during the 90 and 180-day follow-up visit.
3. STUDY DESIGN

3.1 Type and Design of Study
This study is a prospective, single-center clinical trial to be conducted at one clinical site. Up to thirty-five (35) subjects will be treated as follows: Subjects will be enrolled at the investigator’s discretion if they meet inclusion/exclusion criteria and provide written informed consent.

Subjects will be treated using the Ulthera® System by the study investigator or assigned study staff. Investigator and a blinded evaluator will assess baseline cheek, neck and jowl scores on the GAIS scale prior to treatment. Images will be taken immediately prior to treatment and during each follow-up visit using a standardized imaging system. Follow-up visits at 90, and 180 days post-treatment will assess safety and efficacy. GAIS scores will be obtained from the patient at 90-day and 180-day follow-up visits. Scores on Patient Satisfaction Questionnaires completed during the 90-day and 180-day follow-up visits will be obtained and tabulated.

Efficacy will be determined by the overall change in lifting and tightening of the cheek tissue, improvement in jawline definition and improvement in submental skin laxity as measured by the blinded evaluator who will compare baseline, and 90 and 180 day standardized images.

3.2 Study Treatments
This study involves one treatment to be conducted at the screening/treatment visit after obtaining informed consent, screening for inclusion/exclusion criteria, and complying with photography requirements.

3.3 Duration of Study and Rationale
Recruitment for this study may take approximately two months. Following the screening/treatment visit, subjects will be followed for a total duration of 180 days. Therefore, the anticipated total duration of the study is approximately eight months.

3.4 Efficacy Endpoints
Improvement in overall lifting and tightening of skin particularly for the cheek tissue, jawline definition and submental skin laxity, as determined by a masked, qualitative assessment of standardized photographs at 90 and 180 days post-treatment compared to baseline.

The secondary efficacy endpoint of this clinical trial is overall improvement in cheek tissue, jawline definition and submental skin laxity at 3 and 6 months compared to baseline based on the consensus of three masked reviewers. Additionally, patient satisfaction will be measured using a Patient Satisfaction Questionnaire at the 90-day and 180-day follow-up visits.
3.4.1 Photography of Subjects
The clinical response of Ulthera treatment on the face will be assessed by comparing photographic images taken before and after the procedure. All images will be captured using a Canfield System with mirror software, which is an industry-standard photographic system, and digital camera (2D).

3.5 Primary Safety Endpoints
The Ulthera® System was demonstrated to be safe for clinical use when tested in a prior pivotal clinical trial (Protocol Number 1253-014, IDE G060261); however, safety will also be confirmed in the current study. Safety measures include investigator assessment of the initial skin response (e.g., erythema and edema); subject assessment of pain (10-point scale); and routine monitoring of adverse events.

4. STUDY POPULATION
The study population will consist of males and females between 30 and 65 years of age who have a desire for lift and tightening of the cheek tissue and improvement in jawline definition and submental skin laxity. All subjects who have chosen to participate in this clinical trial will be required to sign the informed consent document.

4.1 Informed Consent
Written informed consent will be obtained from all subjects (or their guardians or legal representatives) before any study-related procedures, including any pre-treatment screening procedures, are performed. A draft of the informed consent is provided in Attachment A. Investigators 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, or the IRB-designee 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.
4.2 Eligibility Criteria

4.2.1 Inclusion Criteria
1. Male or female, aged 30 to 65 years.
2. Subject in good health.
3. Subjects who desire lift and tightening of cheek tissue, improvement in jawline definition and/or submental skin laxity.
5. Understands and accepts the obligation not to undergo any other procedures in the areas to be treated through the follow-up period.
6. 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.
7. Subjects of childbearing potential must have a negative urine pregnancy test result at Visit 1 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 the study; b) Without a uterus and/or both ovaries; or c) A bilateral tubal ligation at least six months prior to study enrollment.
8. Absence of physical conditions unacceptable to the investigator.
9. Willingness and ability to provide written consent for study-required photography and requirements (i.e., removal of jewelry and makeup).
10. Willingness and ability to provide written informed consent and HIPAA authorization prior to performance of any study-related procedure.

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

1. Pregnant, lactating, planning to become pregnant, or not using a reliable form of birth control.
2. Presence of an active systemic or local skin disease that may affect wound healing.
3. Severe solar elastosis.
4. Excessive subcutaneous fat on the cheek.
5. Excessive skin laxity on the lower face and neck.
6. Significant scarring in areas to be treated.
7. Significant open facial wounds or lesions.
8. Severe or cystic acne on the face.
9. Presence of a metal stent or implant in the facial area to be treated.
10. Inability to understand the protocol or to give informed consent.
11. Retinoid, microdermabrasion, or prescription level glycolic acid treatments to the intended treatment area within two weeks prior to study participation or during the study.
12. Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
13. History of chronic drug or alcohol abuse.
15. Concurrent therapy that, in the investigator’s opinion, would interfere with the evaluation of the safety or efficacy of the study device.
16. Subjects who anticipate the need for surgery or overnight hospitalization during the study.
17. Subjects who, in the investigator’s opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
18. Concurrent enrollment in any study involving the use of investigational devices or drugs.
19. Current smoker or history of smoking in the last five years.
20. History of the following cosmetic treatments in the facial area to be treated:
   a. Facial skin tightening procedure within the past year;
   b. Injectable filler of any type on the lower 2/3 of the face within the past year;
   c. Botulinum neurotoxin Type A to the lower face and/or neck (platysma) within the past six months;
   d. Ablative resurfacing laser treatment;
   e. Nonablative, rejuvenative laser or light treatment within the past six months;
   f. Dermabrasion or deep facial peels or;
   g. Facelift, blepharoplasty, brow lift, or contour threads.

21. History of using the following prescription medications:
   a. Isotretinoin or other oral systemic retinoids within the past six months;
   b. Coumadin or Heparin, or antiplatelets; or
   c. 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.

5. STUDY PROCEDURES

5.1 Schedule of Assessments at Each Study Visit

Table 5.1-1 provides an overview of the subject screening procedure, baseline evaluation, treatment plan, and follow-up requirements.
Table 5.1-1. Schedule of Baseline and Follow-Up Assessments

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Treatment Day #1</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment/</td>
<td>Immediately post-treatment</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Eligibility assessment</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Demographics and medical history</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy screen</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Investigator skin examination</td>
<td>(2)</td>
<td>√</td>
</tr>
<tr>
<td>Blind evaluator assessments</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Selection/documentation of treatment plan</td>
<td>(3)</td>
<td>√</td>
</tr>
<tr>
<td>Treatment of face</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Subject assessment of pain</td>
<td>(4)</td>
<td>√</td>
</tr>
<tr>
<td>Images</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Follow-up patient satisfaction questionnaire</td>
<td>(5)</td>
<td>√</td>
</tr>
<tr>
<td>Aesthetic Improvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(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
(5) GAIS assessment
(6) Patient Satisfaction Questionnaire

5.2 Pre-treatment Recruiting/Screening
Subjects who meet the enrollment criteria will be selected by the principal investigator from the study site's patient database. Study site personnel will explain the design and purpose of the study to potential study subjects. Subjects interested in participating will meet with study personnel at the study site where informed consent will be obtained.

5.3 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 is not treated with the investigational device because of failure to meet all of the eligibility criteria. Screen failure subjects will not be counted towards the total enrollment of subjects.
5.4 Day of Exposure (Treatment)
Subjects may be treated on the same day that they are screened and provide informed consent.

5.4.1 Pre-treatment Images of Subject's Skin
The images in the study will be obtained using a standardized photographic system. All images will be captured using a standardized photography system for image collection, storage, and analysis. The software identifies each image with a specific label (metadata) that cannot be edited by the user. Only study site personnel and the Sponsor will have access to the subject identifiable Images.

Standard images of the patient’s face will be captured using a digital camera to allow for visualization and quantification of changes in the regions being treated.

The subject's baseline images are taken at this time. These images are considered the pre-treatment comparator images.

5.4.2 Subject Preparation for Treatment
The clinician will first identify the skin areas for which an Ulthera procedure is to be performed (Figure 5.4-1). Treatment records for all regions will be maintained in accordance with this protocol.

Pre-Treatment Medications:
Pre-medication is administered at the discretion of the physician and patient. Comfort is very subjective, and a broad range of sensory responses to an Ulthera® treatment is possible. For example, a patient who has had prior cosmetic treatments may have a higher threshold for pain.

Oral pre-medications must be taken at least 30 minutes prior to treatment and intra-muscular pre-medications must be administered 60 minutes prior to treatment.

30 minutes before treatment:
Valium 5-10mg (1-2 tablets)
Hydrocodone 5/325mg (1-2 tablets)

OR

60 minutes before treatment:
Toradol 60 mg IM
5.4.3 Treatment
The anatomical depth of focal tissue heating is fixed and determined by the set focus depth of a given probe tip, 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. Ulthera will provide the investigator with four types of transducers:

- 7 MHz with a 4.5 mm focal depth
- 7 MHz with a 3.0 mm focal depth
4 MHz with a 4.5 mm focal depth

For treatment of areas where delivery of a low to intermediate level of energy is desired, a specific transducer with a frequency of 7 MHz and a focal depth of 3.0 mm - 4.5 mm will be used.

For treatment areas requiring a higher level of energy, a specific transducer with a frequency of 4 MHz and a focal depth of 4.5 mm will be used. Table 5.4-1 lists the source conditions that we intend to use for this study.

**Table 5.4-1. Source Conditions Used for Protocol ULT-112**

<table>
<thead>
<tr>
<th>Dermal Exposure</th>
<th>Energy Level</th>
<th>Source Conditions (Transducer Choice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial dermis</td>
<td>Low</td>
<td>7 MHz, 3.0 mm focal depth</td>
</tr>
<tr>
<td>Deeper dermis</td>
<td>Intermediate</td>
<td>7 MHz, 4.5 mm focal depth</td>
</tr>
<tr>
<td></td>
<td>Higher</td>
<td>4 MHz, 4.5 mm focal depth</td>
</tr>
</tbody>
</table>

The location to be treated, the transducer, and the energy level will be recorded on the Treatment Parameters System Record.

Prior to initiating treatment, the clinician will assess the subject’s skin tissue based on:
- Demographic factors (age and gender)
- Subject body type based on BMI
- Amount of subcutaneous soft tissue in region to be treated and the area to be treated

The investigator will start the treatment regimen for the protocol-specified area(s), and with a transducer delivering a higher level of acoustic energy (4 MHz, 4.5 mm). Based on the subject's response, the investigator will have the option to continue the treatment at the existing treatment parameters or reduce the treatment energy. Treatment will be delivered in a lined pattern. The subject will be monitored during the treatment.

The investigator will continue the treatment regimen for the protocol-specified area(s) with a second pass using a transducer delivering a minimal or low level of acoustic energy (10 MHz, 1.5 or 7 MHz, 3.0 mm). Based on the subject's response, the investigator will have the option to continue the treatment at the existing treatment parameters or reduce the treatment energy. The subject will be monitored during the treatment.

Ultrasound gel will be applied, the transducer will be placed on the targeted skin surface, and an 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 investigator will place multiple Ulthera exposure lines close to each other (2 to 3 mm) in the selected area, with each line exposure requiring about 5 seconds. Treatment lines can be a maximum length of 25 mm and will produce a series of thermal coagulative zones. The individual zones of thermal coagulation are depicted in Figure 5.4-1 above.

During the treatment procedure, the subject will be asked to rate sensation using a 0 to 10 visual analog scale, with 0 denoting no pain and 10 denoting the most pain possible. This information will be recorded on the Subject Skin Assessment for Pain case report form.

5.4.4 Scoring of Acute Responses
For all exposures, acute responses (e.g., erythema or edema) will be assessed by the investigator and photographically recorded approximately 30 minutes after exposure.

Pain will be assessed by the subject during the treatment. (Subject Pain Assessment Scale, Case Report Form No. 1), using a scale of 0-10 with 0 representing no pain and 10 representing the most pain possible.

Standardized images will be taken at every follow-up visit. These images can be used to provide information about acute responses, if desired.

5.5 Follow-up
Subjects will be asked to return to the clinic for follow-up visits at the protocol-specified intervals. Safety endpoints and adverse events will be monitored at all follow-up visits. Efficacy and patient satisfaction will be recorded.

5.6 Withdrawal Criteria and Procedures
All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue any subject, at any time, if medically necessary. The reason for the subject’s withdrawal should be documented on the appropriate case report form. The subject must undergo the recommended follow-up assessments specified for the last study visit, including an evaluation of disease signs and symptoms, unless contraindicated due to a medical condition. Withdrawn subjects will not be replaced.

5.7 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.

5.8 End of Study (Completion)
All subjects who have signed an informed consent, 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. These discussions will be documented by the investigator and the Sponsor, and reviewed by the monitor.

6. STATISTICAL ANALYSIS

6.1 Efficacy Analysis
The primary analysis of efficacy will be based on the evaluable subjects, hence, only those subjects who have evaluable images at 90 days post treatment will be included in the analysis. Analyses of safety will include all subjects who were treated with the Ulthera® System.

Efficacy will be the proportion of treated subjects determined to improve as stated in the protocol-specified objective and demonstrated with the protocol-specified imaging system.

6.2 Safety Analyses
All adverse events and device-related adverse events will be presented as the numbers of subjects reporting each event.

7. RESTRICTIONS

7.1 Prohibited Medications
Prohibited medications include psychiatric medications deemed inappropriate by the investigator and anticoagulants. Accutane and other systemic retinoids within the past 6 months and topical retinoids, within the past two weeks should not be used.
7.2 Other Restrictions
There are no other restrictions for medication use or other post-treatment care.

8. EVALUATION OF ADVERSE EVENTS

8.1 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.

8.2 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 8.2-1.

Table 8.2-1. Relationship Between Adverse Events and Investigational Device

<table>
<thead>
<tr>
<th>Probably Related</th>
<th>A reasonable causal relationship between treatment with the investigational device and an adverse event is more likely than not.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly Related</td>
<td>A reasonable relationship exists between the device treatment and an adverse event, but the causal relationship is unclear or lacking.</td>
</tr>
<tr>
<td>Not Likely Related</td>
<td>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.</td>
</tr>
<tr>
<td>Unrelated</td>
<td>No relationship between treatment with the investigational device and the adverse event exists.</td>
</tr>
</tbody>
</table>

8.3 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.
8.4 Serious Adverse Events
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 8.6 for severity definitions.)

An adverse event should be classified as serious if it meets any of the following criteria:
   a. results in, or contributes to, a death;
   b. is life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death);
   c. results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure);
   d. requires in-patient hospitalization or prolongs hospitalization;
   e. necessitates medical or surgical intervention to prevent death or a life-threatening condition, or to preclude a permanent disability or incapacity; or
   f. results in a congenital anomaly or birth defect.

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

8.5 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 case report 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.

8.6 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
8.7 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 must report death to the reviewing IRB according to the IRB regulations at the study site.

8.8 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.

9. RISK ANALYSIS

9.2 Minimization of Potential Risks
9.3 Potential Benefits

Potential benefits include lifting and tightening of skin laxity, with results that may contribute to the development of an ultrasound-based, non-invasive tissue-tightening procedure.

9.4 Justification for the Clinical Study

The clinical study is justified by the previous safe clinical experience with the Ulthera® System for facial skin cosmetic applications, and the efficacy in related applications for skin tightening. The study is expected to achieve lifting and tightening of the skin, leading to a positive clinical outcome.

10. DEVICE MANAGEMENT

10.1 Packaging and Labeling

The Ulthera® System will be shipped in a hard case designed for protection during delivery. Upon arrival, Ulthera personnel will set up the system for pre-study testing to ensure proper functioning.

Transducers will be shipped in a separate hard case with additional packaging to protect them, and will be tested by Ulthera personnel to ensure proper functioning prior to use.

10.2 Storage

Shipping and storage conditions include:

Shipping and Storage, System Without Transducers
-20 to 65°C (-4 to 149°F), 15 to 95% relative humidity
500 to 1060 hPa (0.5 to 1.05 ATM)

Shipping and Storage, With Transducers
15 to 30°C (59 to 86°F), 15 to 95% relative humidity
Protect from freezing
500 to 1060 hPa (0.5 to 1.05 ATM)

10.3 Accountability

The investigator or designee must maintain an inventory record of investigational devices received, used for treatment, discarded, and returned to the Sponsor to ensure that the investigational device will not be dispensed to anyone who does not meet the study's criteria.
conditions set forth in this protocol. There will be 100% accountability for all investigational Ulthera® Systems and transducers.

11. 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 CFR Part 812).

11.1 Informed Consent
A sample informed consent document is provided in Attachment A. Informed consent will be obtained from all subjects prior to study participation.

11.2 Institutional Review Board
Prior to initiation of any study procedures, the protocol, informed consent, and device labeling 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 (if necessary) 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.
11.3 Confidentiality of Patient 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 and copy 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 in case report forms. If necessary, their full names may be made known to a regulatory agency or other authorized officials.

12. 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.

12.1 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 and co-investigator's curriculum vitae;
- A letter signed by the chairperson of the IRB of the institution at which the investigation will be conducted indicating that the IRB has reviewed and approved this investigational plan; and
- A copy of the IRB-approved informed consent document.

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 investigational devices, including the type and quantity of devices; the dates of receipt; the lot 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
• case report forms and corrections to the forms
• protocol, amendments, and case report forms
• subject recruiting materials
• Investigator curriculum vitae.

12.2 Investigator Reports
Investigators are required to prepare and submit to the Sponsor the following complete, accurate, and timely reports on this investigation when 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.

12.3 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 in black ink to
case report forms.

Any changes to information in the study progress notes, other source
documents, and case report 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.

12.4 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, 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.

12.5 Records Retention at the Study Site
The investigator is responsible for retaining the necessary records, including
a copy of the protocol, device labeling, case report 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 completed; 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.

13. MONITORING PROCEDURES

13.1 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.

13.2 Pre-Study Monitoring Procedures

13.2.1 Selection of Monitors

There will be an overall study monitor, as well as several other monitors, 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.

13.2.2 Clinical Investigators

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

13.3 Pre-Investigation 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 will ensure 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.

13.4 Periodic Monitoring Visits

- 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 record 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, case report forms and original documents and records such as hospital and clinic charts, consent forms, and operative reports.

All case report forms and other documentation related to the study will be reviewed upon receipt, and the site will be promptly notified of any deficiencies.
13.5 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.

13.6 Study Termination

All routine monitoring functions must be performed prior to the study termination visit; the study termination 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 have been sent to the Sponsor;
• Remind the investigator of the obligation to retain the records; and
• Prepare final monitoring report for Sponsor and IRB.

13.7 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.

13.8 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.

14. CONFIDENTIALITY
15. 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 the judgment of the chairman of the local 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.

16. STUDY INVESTIGATORS

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


ATTACHMENT A: INFORMED CONSENT