Ultherapy

SEE THE BEAUTY OF SOUND

CLINICAL PROTOCOL NUMBER ULT-218

EVALUATION OF THE ULTHERA® SYSTEM FOR TREATING AXILLARY HYPERHIDROSIS

CONFIDENTIAL – PROPRIETARY INFORMATION

DATE: 07SEPTEMBER2016

NCT03320096, redacted
version v1.0, 11Jun2019

SIGNATURE PAGE

Company Name:	Ulthera, Inc., Merz Device Innovation Center (MDIC)
Address:	1840 S. Stapley Drive, Suite 200
	Mesa, AZ 85204
Telephone:	480-619-4069
Toll-Free Telephone:	877-858-4372
Fax:	480-619-4071
Study Device:	Ulthera® System
Protocol Title:	Evaluation of the Ulthera® System for Treating Axillary Hyperhidrosis
Protocol Number:	ULT-218
Draft Revision Date:	03AUG2016
Final Protocol Version Date:	07SEP2016

Ulthera Signature:

This protocol has been reviewed and approved by:

_____ _____

[redacted] Date

[redacted] Quality & Regulatory Affairs

_____ _____

[redacted] Date

[redacted] Clinical & Medical Affairs

_____ _____

[redacted] Date

[redacted] Clinical Affairs

Investigator Signature:

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

_____ _____

Principal Investigator Signature Date

SPONSOR CONTACT INFORMATION

Protocol Title:	Evaluation of the Ulthera® System for Treating Axillary Hyperhidrosis
Protocol Number:	ULT-218
Sponsor:	Ulthera, Inc., Merz Device Innovation Center (MDIC) 1840 S. Stapley Drive, Suite 200 Mesa, Arizona 85204
Clinical & Regulatory Affairs:	[redacted] [redacted] Quality and Regulatory Affairs Phone: [redacted] Fax: [redacted] [redacted] [redacted] Clinical and Medical Affairs Phone: [redacted] Fax: [redacted] [redacted] [redacted] Clinical Affairs Phone: [redacted] Fax: [redacted]

SPONSOR AGREEMENT

Ulthera, Inc. (hereinafter "Study Sponsor") maintains responsibility for the ongoing safety of this clinical trial involving the evaluation of the Ulthera System®. Study Sponsor will promptly notify all investigators, the responsible IRB(s)or Ethics Committee(s) (EC), and the regulatory authorities of any findings from ongoing trial monitoring activities that could adversely affect the safety of subjects, impact the conduct of the clinical study, or alter the IRB's or EC'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) or EC(s) with a copy of a final clinical study report.

INVESTIGATOR AGREEMENT AND CERTIFICATION

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

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

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

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

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

Accepted by:

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

PROTOCOL SYNOPSIS

Company Name:	Ulthera, Inc., Merz Device Innovation Center (MDIC)
Protocol Number:	ULT-218
Protocol Title:	Evaluation of the Ulthera® System for Treating Axillary Hyperhidrosis
Investigational Device:	Ulthera® System
Development Phase:	Pilot
Study Objective:	To evaluate the Ulthera® System and the 7-3.0mm transducer for treating axillary hyperhidrosis.
Study Design:	Prospective, multi-site, non-randomized
Number of Subjects:	N = 20 treated subjects; subjects enrolled may be greater than subjects treated
Study Treatment Groups:	Enrolled subjects will receive treatment at a 3.0mm depth and 0.30 J of energy. Treatment will be delivered in a 3 x 4 grid, 12 treatment squares, delivering 60 lines of treatment per square, i.e., 720 lines per axilla in each treatment (1440 lines total per treatment.)
Subject Population:	Adults between 18 - 75 years of age who meet the inclusion/exclusion criteria.
Inclusion Criteria:	1. Male or female, age 18-75 years. 2. Subject in good health. 3. Diagnosis of bilateral axillary hyperhidrosis refractory to previous topical therapies. 4. At least 50 mg of spontaneous resting axillary sweat production in each axilla measured gravimetrically at room temperature/humidity (20 - 25.6°C/20-80%) over a period of 5 minutes. (Patients should be at rest for at least 30 minutes after physical exercise including walking.) 5. HDSS score of 3 or 4. An attempt will be made to approximate an equal number of scores 3 and 4. 6. Understands and accepts the obligation not to undergo any other procedures in the areas to be treated through the follow-up period. 7. 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. 8. Subjects of childbearing potential must have a negative urine pregnancy test result and must not be lactating at the Screening Visit and be willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study. Women will not be considered of childbearing potential if one of the following conditions is documented on the medical history: a. Postmenopausal for at least 12 months prior to study; b. Without a uterus and/or both ovaries; or c. Bilateral tubal ligation at least six months prior to study enrollment. 9. Absence of physical or psychological conditions unacceptable to the investigator. 10. Willingness to refrain from use of aspirin, Ibuprofen, Naproxen or any other NSAID, and Vitamin E in the 2 weeks prior to each study treatment . 11. Willingness and ability to provide written informed consent prior to performance of any study-related procedure.
Exclusion Criteria:	1. Dermal disorder including infection at anticipated treatment sites in either

	axilla. 2. Previous botulinum toxin treatment of the axilla in the past year. 3. Expected use of botulinum toxin for the treatment of any other disease during the study period. 4. Known allergy to starch powder, iodine, lidocaine, or epinephrine. 5. Secondary hyperhidrosis, for example, hyperhidrosis that is secondary to other underlying diseases including hyperthyroidism, lymphoma and malaria. 6. Previous surgical treatment of hyperhidrosis including sympathectomy, surgical debulking of the sweat glands, subcutaneous tissue curettage and ultrasonic surgery. 7. Unwillingness to wash off antiperspirants and abstain use 72 hours prior to treatments or assessments. 8. Subjects with a history of a bleeding disorder 9. Active implants (e.g., pacemakers or defibrillators), or metallic implants in the treatment areas.) 10. Use of cholinomimetics, anticholinergics, or any oral herbal medicine treatments for hyperhidrosis. 11. Inability to withhold use of antiperspirants or any other topical treatments for hyperhidrosis within 72 hours prior to study treatments and assessments. 12. Unwillingness for complete shaving or removal of underarm hair within 12 hours prior to study treatments and follow-up visits. 13. Women who are pregnant, lactating, possibly pregnant or planning a pregnancy during the study period. 14. Inability to understand the protocol or to give informed consent. 15. History of chronic drug or alcohol abuse. 16. History of chronic or frequently recurring episodic (recurrent episode in past 12 months) autoimmune diseases such as Multiple Sclerosis, Crohn's Disease, Psoriasis, Myasthenia Gravis, Lambert-Eaton Syndrome that has required immune suppressant therapy (such as biologic drug or corticosteroid treatment).. 17. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study device. 18. Subjects who anticipate the need for surgery or overnight hospitalization during the study. 19. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability. 20. Concurrent enrollment in any study involving the use of investigational devices or drugs. 21. Use of antiplatelet agents / Anticoagulants (Coumadin, Heparin, Plavix) in the past 6 weeks; a. Psychiatric drugs that in the investigators opinion would impair the subject from understanding the protocol requirements.
Treatment Outline:	1. Screening/Baseline/Treatment Visit #1: a. Obtain Informed Consent and medical history; b. Screen for general inclusion/exclusion criteria; c. Obtain axillary ultrasound images of each axilla; d. Perform pregnancy screening test, if applicable;

	e. Complete baseline evaluations: HDSS, gravimetric, and starch iodine test with digital images of the result; f. Administer local anesthetic to both axillas; g. Perform bilateral Ultherapy treatment; h. Assess Numeric Rating Scale for Pain; and i. Assess for adverse events. 2. Post-treatment #1 telephone contact: a. Capture adverse events (7±2 days). 3. Treatment Visit #2, 30 ± 7 days post-treatment #1: a. Complete HDSS, gravimetric, and starch iodine test with digital images of the result; b. Perform pregnancy screening test, if applicable; c. Administer local anesthetic to both axillas; d. Perform bilateral Ultherapy treatment; e. Assess Numeric Rating Scale for Pain; and f. Assess for adverse events. 4. Post-treatment #2 telephone contact: a. Capture adverse events (7±2 days). 5. Follow-up Visits post-treatment #2 for efficacy evaluation: a. 30 ± 7 days i. Complete HDSS, gravimetric test, and starch iodine test with digital images of the result; and ii. Assess for adverse events. b. 90 ± 7 days i. Complete HDSS, gravimetric test, and starch iodine test with digital images of the result; ii. Assess for adverse events; and iii. Perform pregnancy screening test, if applicable.
Primary Endpoint:	HDSS score reduction from a 3 or 4 at baseline to a 1 or 2 at 30 days post-treatment #2.
Secondary Endpoints:	1. Reduction in spontaneous axillary sweat production assessed by a gravimetric method at 90 days post treatment #2, as measured by a 50% reduction or more compared to baseline. 2. HDSS score reduction from a 3 or 4 to a 1 or 2 at 90 days post treatment #2. 3. Starch iodine test to assess area of efficacy with digital images.
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. 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. Additional pregnancy screening tests will be performed (if applicable) prior to treatment #2 and at the 180-day follow-up visit.
Study Duration:	Given two months for recruitment and with two study treatments provided 30 days apart, the anticipated study duration is six months.

STUDY OVERVIEW

Evaluation	Screening+	Baseline / Treatment #1+ Day 0	Telephone Contact Day 7±2D Post-Treatment #1	Treatment #2 Day 30±7	Telephone Contact Day 7±2D Post-Treatment #2	Follow-up Intervals Post Treatment #2	
						Day 30±7	Day 90±7
Screening and Subject Consent	√						
Initial Evaluation (Includes entrance criteria, eligibility assessment, demographics, medical history, clinician assessment)	√						
Pregnancy Screen	√^	√^		√^			√
Study Treatment		√		√			
NRS for Subject Pain Assessment		√		√			
HDSS		√		√		√	√
Gravimetric Test	√			√		√	√
Starch Iodine Test and digital images of results		√		√		√	√
Obtain Axillary Ultrasound Images	√						
AE Forms	√	√	√	√	√	√	√

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

^ Pregnancy:

a. If a subject becomes pregnant after the Baseline visit and all study treatments have 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.
c. If a subject becomes pregnant after the Baseline visit but before all study treatments have been completed, additional study treatments should be discontinued and the subject should continue to be followed.

List of Acronyms and Definitions

Term	Definition
AE	Adverse Event
CGAIS	Clinician Global Aesthetic Improvement Scale
CV	Curriculum Vitae
EC	Ethics Committee
Elastosis	Degeneration of the elastic tissues
GAIS	Global Aesthetic Improvement Scale
GCPs	Good Clinical Practices
HDSS	Hyperhidrosis Disease Severity Scale
IRB	Institutional Review Board
MEEI	Massachusetts Eye and Ear Infirmary, Harvard Medical School
NRS	Numeric Rating Scale for pain assessment
PSQ	Patient Satisfaction Questionnaire
RF	Radiofrequency
Rhytidectomy	Mini-facelift
Serious Adverse Event	An adverse event that results in or contributes to death or is life threatening. See Section 7.4 for more detail.
Adverse event severity	The intensity of an adverse event, which can range from mild to moderate to severe. See Section 7.6 for more detail.
SGAIS	Subject Global Aesthetic Improvement Scale
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
US	Ultrasound

TABLE OF 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 trial described in this protocol evaluates clinical outcomes associated with the non-invasive treatment for axillary hyperhidrosis. The investigator will assess the subjects for hyperhidrosis using gravimetric measurement and assess the area of efficacy using a Starch Iodine test. Subjects will evaluate their conditions using the Hyperhidrosis Disease Severity Scale (HDSS) (**Attachment A**).

1.2 BRIEF AGING BACKGROUND AND TREATMENT OVERVIEW

Hyperhidrosis is a disease characterized by perspiration in excess of the physiologic amount necessary to maintain thermal homeostasis[1]. Hyperhidrosis can have very significant effects on patients' lives, causing physical discomfort and social embarrassment and negatively impacting occupational and daily activities.

Primary or idiopathic hyperhidrosis and secondary hyperhidrosis are the two main categories[2]. Patients can have excessive sweating either in a localized area (focal) or over the entire body (generalized). Primary disease is usually focal, affecting the soles, palms, and axillae in various combinations and with varying degrees of severity. Secondary hyperhidrosis can be generalized or focal. In secondary hyperhidrosis the symptoms are due to one of a large number of medical conditions, including endocrine disorders, neurological problems, use of certain drugs, cancer, chronic infections, dermatologic syndromes, and conditions associated with excess catecholamine discharge[3]. Occasionally hyperhidrosis can be seen on the head and face as a primary disorder or become apparent as gustatory sweating secondary to parotid surgery or diabetes. This study focuses on primary hyperhidrosis of the axillae.

Sweat glands in patients with hyperhidrosis are not histopathologically different from those in normal patients, nor is there an increase in the number or size of glands. The condition is caused by hyperfunction of the sweat glands rather than hypertrophy[4]. Patients with primary hyperhidrosis have a higher-than-normal basal level of sweat production as well as an increased response to normal stimuli such as emotional or physical stress.

Humans have up to four million sweat glands distributed over the body, of which about three million are eccrine sweat glands. Eccrine glands secrete an odorless, clear fluid that serves to aid in the regulation of body temperature by allowing heat loss by evaporation. Eccrine glands are in higher density on the soles of the feet and the forehead, followed by the palms and the cheeks.[5, 6] Apocrine sweat glands are located in limited areas—the axilla and urogenital regions—and produce a thick, odorless fluid that undergoes bacterial decomposition, leading to substances with strong odors. The ratio of apocrine to eccrine glands is one to one in the axillae and one to ten elsewhere.[5]

Knowledge of skin and sweat gland anatomy is essential to evaluate each subject (**Figure 1.2-1**), and to develop a treatment plan based on an individual's clinical presentation.

FIGURE 1.2-1. SKIN & SWEAT GLAND ANATOMY

Existing treatment options that have been developed for patients with primary hyperhidrosis can be categorized as non-surgical (topical antiperspirants, iontophoresis, systemic medication) or surgical (endoscopic thoracic sympathectomy, excision of axillary tissue).[1] Botulinum toxin injection, which can be said to be "minimally invasive,"[7] has become a therapy for patients who fail to respond to more-conservative treatment prior to resorting to surgery.[8] The therapeutic alternatives also differ by duration of efficacy, side effects, and response rate in the various anatomic areas treated.

Topical therapy for focal hyperhidrosis, or antiperspirant treatment, can be carried out with chemicals of several different classes—astringent agents, topical anticholinergics, local anesthetics, and aluminum and other metallic salt solutions.[9] The general population in industrialized nations uses over-the-counter antiperspirants for cosmetic control of underarm sweating and odor, but patients with moderate-to-severe hyperhidrosis need stronger therapy. Prescription products as well as specially compounded solutions are often needed for these patients,[10] but are not always effective.[11] Other than aluminum chloride, many of the topical agents reviewed are not available commercially or do not have U.S. Food and Drug Administration approval for the treatment of hyperhidrosis.

Iontophoresis is defined as the passing of an ionized substance through intact skin by the application of a direct electrical current.[12] Tap water iontophoresis is considered by many dermatologists to be the first line of treatment for hyperhidrosis of the palms and soles.[13] Although more cumbersome, iontophoresis can be used to treat axillary hyperhidrosis as well. In addition to simple tap water iontophoresis, clinicians have also used iontophoresis to deliver anticholinergics and other drugs to areas affected by hyperhidrosis.[14] Two iontophoresis devices currently available in the US, the Drionic and the Fischer Model MD-1a Iontophoresis unit, have received US Food and Drug Administration approval for treating hyperhidrosis.

Botulinum toxin A injection has been used successfully to reduce excessive sweating in all of the body areas affected in primary hyperhidrosis: axillary, palmoplantar, and facial/gustatory. Characterized as a "minimally invasive treatment option" compared to local surgery and endoscopic thoracic sympathectomy, the use of botulinum toxin has become an important treatment option for patients not responding to more conservative therapies.[7] Botulinum toxin A has been approved for use in hyperhidrosis in Canada, the U.K. and other countries in Europe and South America (more than 23 countries total). In 2004, the US Food and Drug Administration (FDA) approved botulinum toxin type A for the treatment of severe primary axillary hyperhidrosis in patients unable to obtain relief using antiperspirants.

Systemic medication can be used for the treatment of generalized or focal hyperhidrosis.[10] Many of the drugs reported useful for hyperhidrosis have not been studied in controlled trials, their use being based only on anecdotal evidence. Furthermore, at the doses likely to inhibit hyperhidrosis, side effects can be limiting.[12] In addition many of these drugs are not approved by the US Food and Drug Administration specifically for the treatment of hyperhidrosis.

The most invasive treatment for hyperhidrosis is the surgical interruption of the thoracic sympathetic chain, a procedure done with the goal of permanently stopping sweating in the area innervated by the involved ganglia. Sympathectomy has been shown to be very effective for palmar sweating, but is less effective for axillary symptoms.[1] Although now done as a minimally invasive technique using video-assisted endoscopy, the procedure is still associated with complications that lead most clinicians to reserve this procedure for patients with severe symptoms who have failed to improve with more-conservative treatment.[10]

Treatment of severe hyperhidrosis by excision of sweat glands is clearly only feasible for axillary disease. The eccrine sweat glands are located in the deep dermis and in the upper subcutaneous layer.[15] There have been many different procedures used to remove axillary sweat glands; they can be grouped into three major categories.[16] Excision of both skin and underlying sweat glands is the most radical approach. Removing subcutaneous glands through a small incision by scraping the glands from the undersurface of the dermis with a curette or by liposuction are two major variants of the same approach. The third category is a mixture of the first two—a limited central excision is combined with curettage of the surrounding axillary subcutaneous glands.[1] All of these procedures can be done under tumescent local anesthesia.

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.

As stated earlier, it is hypothesized that the creation of focal lesions at the depth of the sweat glands, will effectively damage the glands without surface effects and result in a reduction of sweat.

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**

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 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[17].

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**.

For this study a new 7 MHz transducer will be used, treating at a 3.0mm depth.

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**. When the system was initially launched, energy level 4 (EL4) was the default level. Since then, studies have demonstrated in human subjects that lowering energy levels from EL4 to EL2 has mitigated pain scores by 26% without compromising efficacy. The energy level to be used for this study will be EL2 (0.30J) using a new DS 7-3.0 transducer.

TABLE 1.4-2 TRANSDUCER ENERGY LEVELS

TRANSDUCER	ENERGY LEVELS [J]				
	LEVEL 4	LEVEL 3	LEVEL 2	LEVEL 1	LEVEL 0
DS 4 - 4.5	1.20	1.00	0.90	0.75	0.00
DS 7-4.5	1.05	0.90	0.75	0.66	0.00
DS 7 - 3.0	0.45	0.35	0.30	0.25	0.00
DS 7 - 3.0N	0.45	0.35	0.30	0.25	0.00
DS 10-1.5	0.25	0.20	0.18	0.15	0.00
DS 10-1.5N	0.25	0.20	0.18	0.15	0.00

1.5 PRECLINICAL STUDIES

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

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

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

1.6 CLINICAL STUDIES

Three clinical studies have been conducted using the Ulthera® System: a clinical safety study at MEEI (Protocol Number 05-06-032), a pivotal study at Northwestern University in Chicago (Protocol Number 1253-014, IDE G060261), and a clinical safety and effectiveness Study at the University of Texas Southwestern Medical Center (UTSW) (Protocol Number 00000404). During these studies, in which the Ulthera® System was extensively used, safe and efficacious energy delivery protocols were established.

1.6.1 CLINICAL SAFETY STUDY AT MEEI

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

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

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

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

1.6.2 CLINICAL SAFETY AND EFFECTIVENESS STUDY AT NORTHWESTERN UNIVERSITY

A prospective, open-label clinical study was conducted at Northwestern University (Protocol Number 1253-014, G060261). The study was approved by the IRB at Northwestern University, and all subjects signed the informed consent document. The objectives of this clinical study were to: 1) demonstrate the safety of the Ulthera®

treatment and 2) achieve eyebrow elevation resulting from tissue coagulation and tightening. Thirty-five subjects were enrolled in the study. Enrolled subjects were of either sex over the age of 21, who had a desire to obtain an improvement of eyebrow elevation and had chosen to receive an Ultherapy™ treatment. Enrollment was open to all skin types (Fitzpatrick 1-VI).

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

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

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

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

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

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

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

Study subjects were assessed for adverse events immediately post-procedure, and then at 60, 90 and 180 days. A total of seven adverse events were reported; however, only three were considered device/procedure related

(welting of the skin within the treated area). All of the events resolved with no residual sequelae. The three device related adverse events were considered mild in nature.

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

This study demonstrated that Ultherapy® is safe and efficacious for the improvement in submental *(beneath the chin)* and neck skin laxity.

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

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

Upon analysis of all the photographs used in the clinical study, 54 of 108 day 180 photos were identified as having inconsistencies in photo quality (changes in lighting, color, focus, patient positioning, cropping, etc.). Therefore a sub-set analysis was conducted using the primary endpoint of masked assessment on the remaining 54 day 108 evaluable photo sets that were deemed the most consistent in photo quality. The results of the sub-set analysis demonstrated improvement of lines and wrinkles based on masked assessment of pre- and post-treatment photographs in 36 of 54 (~67%) evaluable subjects with the most consistent photo quality after one Ultherapy® treatment 180 days post-treatment. Subjects' overall aesthetic improvement was based on CGAIS assessment by the study clinician. Subjects rated at some degree of improvement *(very much improved, much improved or improved)* were 76% and 65% at 90 and 180 days, respectively. Patient satisfaction questionnaires (PSQ), completed at 90 and 180 days post-treatment captured whether subjects were satisfied with their Ultherapy® treatment and if they noticed improvement in their décolleté area. At 90 days, 62% and 81% of the subjects were satisfied with their Ultherapy® treatment and noticed improvement in their décolleté area, respectively. This response continued through 180 days post-treatment, where 65% and 85% of the subjects were satisfied and noticed improvement in their décolleté area, respectively. Device safety was demonstrated as there were no serious adverse events (SAEs) or unanticipated adverse device effects (UADEs) related to treatment with the

Ulthera System. Of the adverse events, all but two were mild. Only two events were moderate, one of which was not device-related. All events resolved.

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

1.6.5 HYPERHIDROSIS PILOT STUDY

A randomized, double-blind, controlled pilot study was conducted to evaluate the efficacy and safety of the Ulthera® System for the treatment of primary axillary hyperhidrosis. The objective of study was to evaluate the efficacy and safety of the Ulthera® System for treatment of primary axillary hyperhidrosis.

Twenty subjects meeting inclusion and exclusion criteria were enrolled. These criteria included a score of 3 or 4 on the Hyperhidrosis Disease Severity Scale (HDSS) as well as >50mg/5 min of sweat production in both axilla as measures by gravimetric method. Active-treated subjects (N=12) received two treatments 28 days apart consisting of 240 lines each, using both 4MHz-4.5mm and 7MHz-3.0mm transducers, for a total of 480 lines per axilla. No energy was delivered during a similar treatment for Sham-treated subjects (N=8). Both groups received pre-treatment injections of lidocaine plus epinephrine. Efficacy at 7, 14, 30, 37, 44, 60, 90, and 120 days was measured by Hyperhidrosis Disease Severity Scale, gravimetric sweat production, and starch iodine test. Patient satisfaction was assessed at 30, 60, and 90 days (trial days 60, 90 and 120) after second treatment. The primary endpoint was response at 60 days (30 days after second treatment), defined as HDSS score of 1 or 2. Adverse events were collected at all follow-up time points and spontaneous reports were also collected.

Subjects were an average age 34 (range 21-52), 30% were female, 30% Caucasian, 50% Hispanic/Latino, 15% African American, and 5% Asian. No subjects responded to sham treatment, either at the primary endpoint visit or at any other visit throughout the study.

At 30 days after second treatment (day 60 of trial), the response rate, as measured by HDSS, in the active treatment group was 67%, a significant difference compared to 0% in the sham group ($p = 0.005$, two-sided Fisher's exact test (FET)). Response to active treatment peaked 7 days after the second treatment (83%) and was sustained for the remainder of the trial. Ninety days after the second treatment (day 120 of the trial), 67% of subjects were still in response. Gravimetric measurement of sweat production showed similar results. At all follow-up study visits, sweat production decreased from baseline by at least 50% in the active treatment group but not in the sham group. Regardless of study visit, percent change from baseline in gravimetric measurement was significantly greater in the active treatment group than in the sham group ($p < 0.0001$, rank-based repeated measures analysis of variance). In the active treatment group, the greatest change from baseline (73.1%) was at 90 days after the second treatment (day 120 of the trial). Starch iodine testing qualitatively supported a reduction in sweat production in the active-treated subjects compared to sham-treated subjects. All but one subject at 30 and 90 days after second treatment and two subjects at 60 days after second treatment in the active-treated group were satisfied or very satisfied. None of the sham-treated reported satisfaction at any time point after the second treatment. Treatment-related AEs reported in the active-treated group were bruising in 3 subjects (15%) with an average duration of 3.3 days (range 2-5 days), soreness or tenderness in subjects (83%) lasting an average of 12.9 days (range 4-31 days) during which only 2 subjects took a single dose of ibuprofen the day after treatment, numbness in 1 subject (8%) lasting 13 days, and paresthesia in 3 subjects (25%) lasting an average of 13.3 days (range 10-18 days). Treatment related AEs reported in the sham-treated group were soreness in 2 subjects (25%) lasting1 day, and paresthesia in 1 subject (12.5%) lasting 1 day. Average pain scores for both transducers during both treatments for the sham-treated group were 0.8 (range 0-5) while pain scores averaged 1.8 (range 0-5 for the active-treated group suggesting that blinding was sufficient.

Pilot study results suggest the Ulthera® System may be efficacious and safe for the treatment of axillary hyperhidrosis.

2. Study Objective and Design

2.1 Study Objective

The objective of this study is to evaluate the effect of Ultherapy using the 7-3.0mm transducer on axillary sweat glands.

2.2 Type and Design of Study

This study is a prospective, multi-center, non-randomized clinical trial. Up to 20 subjects who are naïve to Ultherapy for treatment of hyperhidrosis will be enrolled if all entrance criteria are met confirming eligibility for study treatment. Subjects will be treated using the Ulthera® System by the study investigator, sub-investigator or delegated clinician, receiving treatment in a 3 x 4 grid, 12 treatment squares, 60 lines of treatment per square, at one treatment depth (3.0mm), at 0.30 J of energy.

Ultrasound images will be captured of each axilla prior to the first study treatment to assess dermal thickness and depth of sweat glands. A gravimetric measurement of sweat production, starch iodine test, and pregnancy screening test, if applicable, will be performed prior to each study treatment. Digital images of the starch iodine test will be obtained. HDSS scores will be obtained prior to each treatment. During treatment, the average Numeric Rating Scale (NRS) score will be obtained by axilla treated.

Following the completion of study treatment(s), follow-up visits will be at 30, and 90 days post-treatment to assess safety and efficacy. Gravimetric sweat production measures and starch iodine tests will be completed at treatment visit #2 and at all follow-ups for all study groups. Digital images of the starch iodine test will be obtained. HDSS scores will be obtained at the treatment visit(s) and at all follow-ups for all study groups.

Efficacy will be determined by HDSS score reduction from a 3 or 4 at baseline to a 1 or 2 at 30 days post-treatment. Subject Gravimetric results, Starch iodine results, and HDSS scores at all follow-ups will also be analyzed as secondary outcomes.

2.3 Duration of Study

Recruitment for this study may take approximately two months. Subjects will receive two study treatments provided 30 days apart. Following the treatment visit #2, subjects will be followed for a total duration of 90-days. Therefore, the anticipated total duration of the study is approximately six months.

3. Study Procedures

3.1 Schedule of Assessments at Each Study Visit

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

TABLE 3.1-1 SCHEDULE OF ASSESSMENTS

Evaluation	Screening+	Baseline / Treatment #1+ Day 0	Telephone Contact Day 7±2D Post-Treatment #1	Treatment #2 Day 30±7	Telephone Contact Day 7±2D Post-Treatment #2	Follow-up Intervals Post Treatment #2	
						Day 30±7	Day 90±7
Screening and Subject Consent	√						
Initial Evaluation (Includes entrance criteria, eligibility assessment, demographics, medical history, clinician assessment)	√						
Pregnancy Screen	√^	√^		√^			√
Study Treatment		√		√			
NRS for Subject Pain Assessment		√		√			
HDSS		√		√		√	√
Gravimetric Test	√			√		√	√
Starch Iodine Test and digital images of results		√		√		√	√
Obtain Axillary Ultrasound Images	√						
AE Forms	√	√	√	√	√	√	√

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

^ Pregnancy:

a. If a subject becomes pregnant after the Baseline visit and all study treatments have 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.
c. If a subject becomes pregnant after the Baseline visit but before all study treatments have been completed, additional study treatments should be discontinued and the subject should continue to be followed.

4. Subject Selection and Pre-Treatment

The study population will consist of males and females between 18 and 75 years of age who have a desire to temporarily reduce their hyperhidrosis symptoms and all subjects who have chosen to participate in this clinical trial as evidenced by execution of the informed consent document. Subjects enrolled will include those naïve to Ultherapy® for treatment of hyperhidrosis who will receive two Ultherapy® treatments at a 3.0mm depth, 30 days apart.

4.1 PRE-TREATMENT RECRUITING/SCREENING

Subjects will be recruited from the study site's patient database and screened. 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 their guardians 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 or EC. Each Informed Consent Form will include the elements required by FDA regulations in 21 CFR Part 50.

The IRB- or EC-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 18-75 years.
2. Subject in good health.
3. Diagnosis of bilateral axillary hyperhidrosis refractory to previous topical therapies.
4. At least 50 mg of spontaneous resting axillary sweat production in each axilla measured gravimetrically at room temperature/humidity (20 - 25.6°C/20-80%) over a period of 5 minutes. (Patients should be at rest for at least 30 minutes after physical exercise including walking.)
5. HDSS score of 3 or 4. An attempt will be made to approximate an equal number of scores 3 and 4.
6. Understands and accepts the obligation not to undergo any other procedures in the areas to be treated through the follow-up period.
7. 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.
8. Subjects of childbearing potential must have a negative urine pregnancy test result and must not be lactating at the Screening Visit and be willing and able to use an acceptable method of birth control (e.g. barrier methods used with a spermicidal agent, hormonal methods, IUD, surgical sterilization, abstinence) during the study. Women will not be considered of childbearing potential if one of the following conditions is documented on the medical history:
    a. Postmenopausal for at least 12 months prior to study;
    b. Without a uterus and/or both ovaries; or
    c. Bilateral tubal ligation at least six months prior to study enrollment.
9. Absence of physical or psychological conditions unacceptable to the investigator.

10. Willingness to refrain from use of aspirin, Ibuprofen, Naproxen or any other NSAID, and Vitamin E in the 2 weeks prior to each study treatment.
11. Willingness and ability to provide 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. Dermal disorder including infection at anticipated treatment sites in either axilla.
2. Previous botulinum toxin treatment of the axilla in the past year.
3. Expected use of botulinum toxin for the treatment of any other disease during the study period.
4. Known allergy to starch powder, iodine, lidocaine, or epinephrine.
5. Secondary hyperhidrosis, for example, hyperhidrosis that is secondary to other underlying diseases including hyperthyroidism, lymphoma and malaria.
6. Previous surgical treatment of hyperhidrosis including sympathectomy, surgical debulking of the sweat glands, subcutaneous tissue curettage and ultrasonic surgery.
7. Unwillingness to wash off antiperspirants and abstain use 72 hours prior to treatments or assessments.
8. Subjects with a history of a bleeding disorder
9. Active implants (e.g., pacemakers or defibrillators), or metallic implants in the treatment areas.)
10. Use of cholinomimetics, anticholinergics, or any oral herbal medicine treatments for hyperhidrosis.
11. Inability to withhold use of antiperspirants or any other topical treatments for hyperhidrosis within 72 hours prior to study treatments and assessments.
12. Unwillingness for complete shaving or removal of underarm hair within 12 hours prior to study treatments and follow-up visits.
13. Women who are pregnant, lactating, possibly pregnant or planning a pregnancy during the study period.
14. Inability to understand the protocol or to give informed consent.
15. History of chronic drug or alcohol abuse.
16. History of chronic or frequently recurring episodic (recurrent episode in past 12 months) autoimmune diseases such as Multiple Sclerosis, Crohn's Disease, Psoriasis, Myasthenia Gravis, Lambert-Eaton Syndrome that has required immune suppressant therapy (such as biologic drug or corticosteroid treatment)..
17. Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study device.
18. Subjects who anticipate the need for surgery or overnight hospitalization during the study.
19. Subjects who, in the investigator's opinion, have a history of poor cooperation, noncompliance with medical treatment, or unreliability.
20. Concurrent enrollment in any study involving the use of investigational devices or drugs.
21. Use of antiplatelet agents / Anticoagulants (Coumadin, Heparin, Plavix) in the past 6 weeks;
22. Psychiatric drugs that in the investigators opinion would impair the subject from understanding the protocol requirements.

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

4.4 Screen Failures

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

4.5 Subject Randomization and Treatment Group Assignment

Subjects are not randomized in this study. They will all be treated using the same treatment approach (see Section 5.1 for Study Treatment details).

4.6 Study Images

Ultrasound images will be obtained of each axilla using the Ulthera® System at baseline. All starch iodine tests will be captured with digital images. All images will be captured using a 2D digital imaging system.

5. Treatment of Subjects and Follow-up

This study involves two treatments 30 days apart completed at the treatment visit #1 and treatment visit #2 after obtaining informed consent, screening for inclusion/exclusion, confirming the completion of a washout period of at least 2 weeks from use of aspirin, Ibuprofen, Naproxen or any other NSAID, and Vitamin E, if applicable, complying with protocol specified photography requirements, completing a pregnancy test, if applicable, and completing any study specific baseline assessments.

5.1 Study Treatment

5.1.1 Transducers

One transducer will be used during this trial – a 7 MHz transducer with 3.0mm focal depth.

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

5.1.2 Pre-Treatment Medications

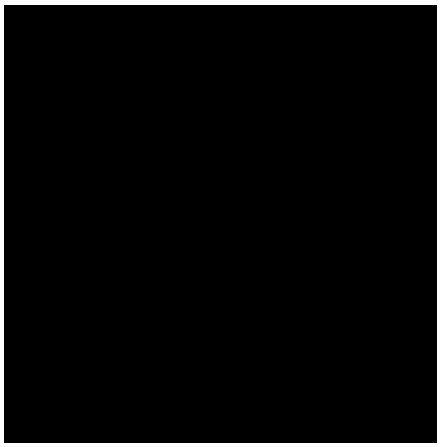
All study subjects will receive injections of 1% lidocaine with epinephrine to each axilla prior to each study treatment.

5.1.3 Subject Preparation for Treatment

a. The investigator, sub-investigator, or delegated clinician will first assess the subject's hyperhidrosis based on:
    - Starch iodine test
    - Amount of subcutaneous soft tissue in region to be treated and the area to be treated

The treatment map identifies the areas and pattern where the 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.

FIGURE 5.1.3-1 TARGET TREATMENT AREAS



5.1.4 TREATMENT

All study treatments will be performed by the investigator, sub-investigator, or delegated clinician (i.e., study treatment clinician as designated by the principal investigator.)

Ultrasound gel will be applied to the transducer, which will then 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 appropriate 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**) above will be administered in a 3 x 4 grid (minimum), resulting in at least 12 treatment squares, depending on the size of each subject's axilla. Two Ultherapy® treatments will be provided at a 3.0mm depth, 30 days apart. At each treatment, study subjects should receive a minimum of 720 treatment lines, +10% variance, to each axilla (minimum of 1440 total lines of treatment for both axillae) delivering 60 treatment lines per treatment square. **The treatment lines must be delivered in multiple passes, with no more than 10 lines delivered per treatment square with each pass, for a total of at least 6 passes per square**. When delivering passes of treatment, all 12 treatment squares should be treated with 10 lines in sequential order (square 1, square 2 and so on), then once complete with the first pass the sequence is followed again to deliver a second pass of 10 lines per square until all 6 passes of 10 lines per square are completed.

The purpose of specifying the number of lines per pass and number of total passes is to minimize the risk of adverse events (AE). In a prior clinical trial, it was observed that AE rates were lower when this high-density treatment was delivered as stated above. 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. Short-term post-treatment adverse events will be assessed via phone contact with study subjects following each study treatment at 7±2 days post-treatment.

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 B**). Pain scores should be obtained following each completed pass for each axilla treated. The average pain score for the entire axilla treated will then 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. Additional pregnancy screening tests will be performed (if applicable) prior to treatment #2 and at the 90-day follow-up visit.

5.3 OUTCOME MEASURES

The Hyperhidrosis Disease Severity Scale (HDSS)

The Hyperhidrosis Disease Severity Scale (HDSS) (**Attachment A**) is a validated scale used for primary axillary/underarm hyperhidrosis patients. It provides a qualitative measure of the severity of their condition based on how it affects their daily activities. Patients select the statement that best reflects their experience with underarm sweating. It is a 4-point scale, with the following descriptors:

1. My underarm sweating is never noticeable and never interferes with my daily activities
2. My underarm sweating is tolerable but sometimes interferes with my daily activities
3. My underarm sweating is barely tolerable and frequently interferes with my daily activities
4. My underarm sweating is intolerable and always interferes with my daily activities

Gravimetric Sweat Production

Reduction of at least 50% from baseline in the average spontaneous axillary sweat production per subject (left and right axilla), i.e., up to 40 data points per time point, assessed by gravimetric method.

Gravimetric method is performed by drying the surface of the skin, then applying a pre-weighed filter paper to the axilla for a period of time (5 min) measured by a stopwatch. The paper is then weighed and the rate of sweat production is calculated in mg/5 min based on the difference in end weight and pre-weight.

Start Iodine Test

Performed to assess area of efficacy. Starch Iodine test is performed by applying an iodine solution to the sweaty area. After it dries, starch is sprinkled on the area. The starch-iodine combination turns a dark blue color wherever excess sweat is present. Digital images of the starch iodine test will be obtained.

5.3.1 PRIMARY ENDPOINT

The primary endpoint of this study is HDSS score reduction from a 3 or 4 at baseline to a 1 or 2 at 30 days post-treatment #2.

5.3.2 SECONDARY ENDPOINTS

The secondary endpoints of this clinical trial include:

1. A reduction in spontaneous axillary sweat production assessed by gravimetric method at all time points following completion of study treatment(s), as measured by a 50% reduction or more compared to baseline.

   a. Gravimetric method is performed by drying the surface of the skin, then applying a pre-weighed filter paper to the axilla for a period of time measured by a stopwatch. The paper is then weighed and the rate of sweat production is calculated in mg/min.
2. HDSS score reduction from a 3 or 4 to a 1 or 2 at 90 days post treatment #2.
3. Starch iodine test to assess area of efficacy.
   a. Starch Iodine test is performed by applying an iodine solution to the sweaty area. After it dries, starch is sprinkled on the area. The starch-iodine combination turns a dark blue color wherever excess sweat is present. Digital images of the starch iodine test will be obtained.

5.4 FOLLOW-UP

Subjects will be asked to return to the clinic for follow-up visits at 30 and 90 days post-treatment #2.

The following assessments will be completed at all follow-up visits: gravimetric assessment, starch iodine test, and HDSS. Digital images of the starch iodine test will be obtained. At the last follow-up visit, a pregnancy screening test will be completed, if applicable. Safety endpoints and adverse events will be monitored at all follow-up visits.

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 or EC 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 complete the study duration will be considered to have completed the study. Any subject who does not return for a scheduled follow-up visit will be contacted at least twice by telephone to determine the cause for the missed visit and to try to get the subject scheduled for the follow-up. A new visit will be scheduled as soon as possible. All subjects should be followed until completing the study follow-up or until study discontinuation (withdrawal) for other reasons. The reason for study discontinuation should be documented for each subject. Subjects will be deemed "Lost-to-Follow-up" if they have not returned within six weeks after the last

follow-up target. For any subject lost to follow-up at least three attempts to contact the subject must be documented; the attempts must be two phone calls/emails and a registered letter.

6. Statistical Analysis

For a given parameter, data will be summarized for each time point for which data for that parameter are available. Summaries will be displayed by time point. Subjects with incomplete data will be included in summaries for which they have data available. Baseline will be defined as the most recent observation before the first treatment. 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. For the primary efficacy outcome, two-sided 95% confidence intervals will be calculated for differences in proportions between study groups. All programs for data output and analyses will be written in SAS® version 9.2 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 a follow-up visit at 30-days post-treatment #2 will be included in the analysis using the Last Value Carried Forward method. Analyses of safety will include all subjects who received (complete or incomplete) study treatment.

Efficacy will be the proportion of treated subjects determined to be improved by the reduction in the number of sweat glands from baseline to 30-days post-treatment #2.

6.2 Safety Analyses

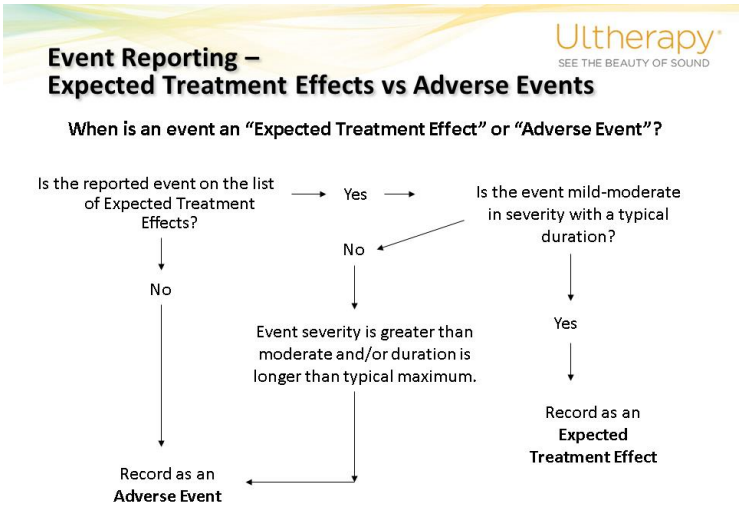
All adverse events and device related adverse events will be presented as the number of subjects reporting each event.

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, defined as: any typical treatment side-effect of Ultherapy® of mild to moderate severity and lasting up to a typical maximum duration (See **Table 8.1.1** for typical maximum durations), or as 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 IRB OR 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:

Death

Death was an outcome of the adverse event.

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.

Hospitalization (initial or prolonged)

Admission to the hospital or prolongation of hospitalization was a result of the adverse event.

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.

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.

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.

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 or EC according to the IRB or EC 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 or EC according to the IRB or EC 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 in **Table 8.1.1** 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 1 week
Acute Pain	Immediate/momentary (while energy is being delivered) - 2 hours
Induration	Up to 12 weeks
Pruritus	Up to 2 weeks
Welting/Raised Areas of Edema	Up to 4 weeks
Skin Burn, Scarring, Change in pigmentation	Up to 8 weeks
Tenderness/Soreness/Pain/Sensitivity to Touch	Up to 3 weeks
/Muscle Twitching/Tingling/Paresthesia/Numbness	Up to 5 weeks
Reduced Range of Motion	Up to 3 weeks
Skin Peeling	Up to 2 weeks

Additional potential risks include: nerve injury, arterial blood spasm, change in axilla odor, and reduction of underarm hair growth.

The risks from lidocaine with epinephrine may include pain and discomfort from the injections, infection at the anesthetic site, lightheadedness, nervousness, mood change, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, tremors, seizures, or unconsciousness. Additional uncommon side effects may include bradycardia, hypotension and cardiac arrest. Allergic reactions may appear as skin rashes, swelling or anaphylaxis.

Risk associated with a starch iodine test may include an allergic reaction to iodine solution or starch powder. No risks are anticipated from completion of a gravimetric sweat test or ultrasound imaging.

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 temporary relief of axillary hyperhidrosis symptoms. Results of the study may contribute to developing an ultrasound-based, non-invasive axillary hyperhidrosis procedure.

8.4 Justification for the Clinical Study

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

9. Device Management

9.1 Packaging

On a site-specific basis, the Ulthera® System will be shipped in a hard case designed to protect the system during delivery.

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) or Ethics Committee Regulations (ICH Guidelines); 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 OR ETHICS COMMITTEE

Prior to initiation of any study procedures, the protocol, informed consent, and operators manual will be submitted to a duly constituted IRB or EC for view and approval. In addition, any amendments to the protocol or Informed Consent Form will be reviewed and approved by the IRB or EC. The Sponsor must receive a letter documenting IRB or EC 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 or EC during the course of the clinical study. These reports will include:

- Informing the IRB or EC 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 or EC.

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

10.3 CONFIDENTIALITY OF SUBJECT RECORDS

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

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

11. REPORTS AND RECORDS MANAGEMENT

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

11.1 INVESTIGATOR RECORDS

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

- Investigator Agreement, signed by the investigator, which lists any physicians who will be involved in conducting the investigation under the direction of the primary investigator;
- A copy of the principal investigator's, sub-investigator's, other delegated study clinicians' curriculum vitae;
- A letter signed by the chairperson of the IRB or EC overseeing the conduct of this study indicating that the IRB or EC has reviewed and approved this investigational plan; and
- A copy of the IRB- or EC-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 or EC of a subject death as specified by the IRB or EC.
- 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 or EC 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 or EC 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 or EC at regular intervals and at least on an annual basis.
- The investigator will notify the Sponsor and reviewing IRB or EC 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 or EC 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 or EC within three months after termination or completion of the study.
- The investigator will provide any other information upon the request of an IRB or EC, FDA, or the Sponsor.

11.3 DATA COLLECTION

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

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

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

11.4 SOURCE DOCUMENTS

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

11.5 Records Retention at the Study Site

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

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

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

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

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

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

12. Monitoring Procedures

12.1 Monitoring

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

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

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

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

12.2 Pre-Study Monitoring Procedures

12.2.1 Selection of Monitors

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

12.2.2 Clinical Investigators

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

12.3 Site Initiation Visit

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

- Understands the requirements for a well-controlled study;
- Understands the clinical protocol;
- Understands his/her reporting obligations;
- Understands the requirements for device accountability;
- Understands and accepts the obligations to obtain informed consent in accordance with 21 CFR Parts 50 and 56;
- Understands and accepts the obligation to obtain IRB or EC review and approval of the clinical investigation before it is initiated and to ensure continuing review of the study by the IRB or EC in accordance with 21 CFR Part 56, and to keep the Sponsor informed of all IRB or EC 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 or EC 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 or EC 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 or EC and Sponsor.
- The appropriate staff is conducting study activities.

The investigator or designee must, upon request, provide to the Sponsor or FDA investigator the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, study-specific

data forms and original documents and records such as clinic charts, subject informed consent forms, and treatment reports.

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

12.5 Frequency of Monitoring Visits

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

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

Each site will undergo a monitoring visit 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 and IRB or EC.

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. PREMATURE TERMINATION OR SUSPENSION OF THE INVESTIGATION OR AN INVESTIGATION SITE

The investigation or an investigation site can be prematurely terminated or suspended by the sponsor. Reasons for termination of the investigation or an investigation site may include, but are not limited to, the following:

- Subject enrolment is unsatisfactory.
- The risks and benefits of continuing the investigation have been reassessed, and the risks outweigh any potential benefits.
- The incidence of AEs constitutes a potential health hazard to the subjects.
- New scientific data on the device do not justify a continuation of the investigation.
- The investigator or investigation site exhibit serious and/or persistent non-adherence to the clinical protocol, the Declaration of Helsinki, EN ISO 14155, and/or applicable regulatory requirements.
- The sponsor decides to terminate the investigation at any time for any other reason.
- Furthermore, the investigation may be prematurely ended if the regulatory authority or the EC has decided to terminate or suspend approval for the investigation, the investigation site, or the investigator.

If the investigation is prematurely terminated or suspended for any reason, the investigator must inform the subjects and assure appropriate follow-up treatment. Within the timeframes noted in applicable regulations, the sponsor will promptly inform the investigators, investigation sites, the EC, and regulatory authorities of the termination or suspension of the investigation, as well as provide reasons for the action. The sponsor will notify the administration departments of clinical investigation of all clinical trial institutions within five days, and specify reasons in a written form.

14. 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.

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 or EC, 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 or EC 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 or EC identified with this responsibility. Except for “administrative amendments”, investigators must await IRB or EC 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 or EC, 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.

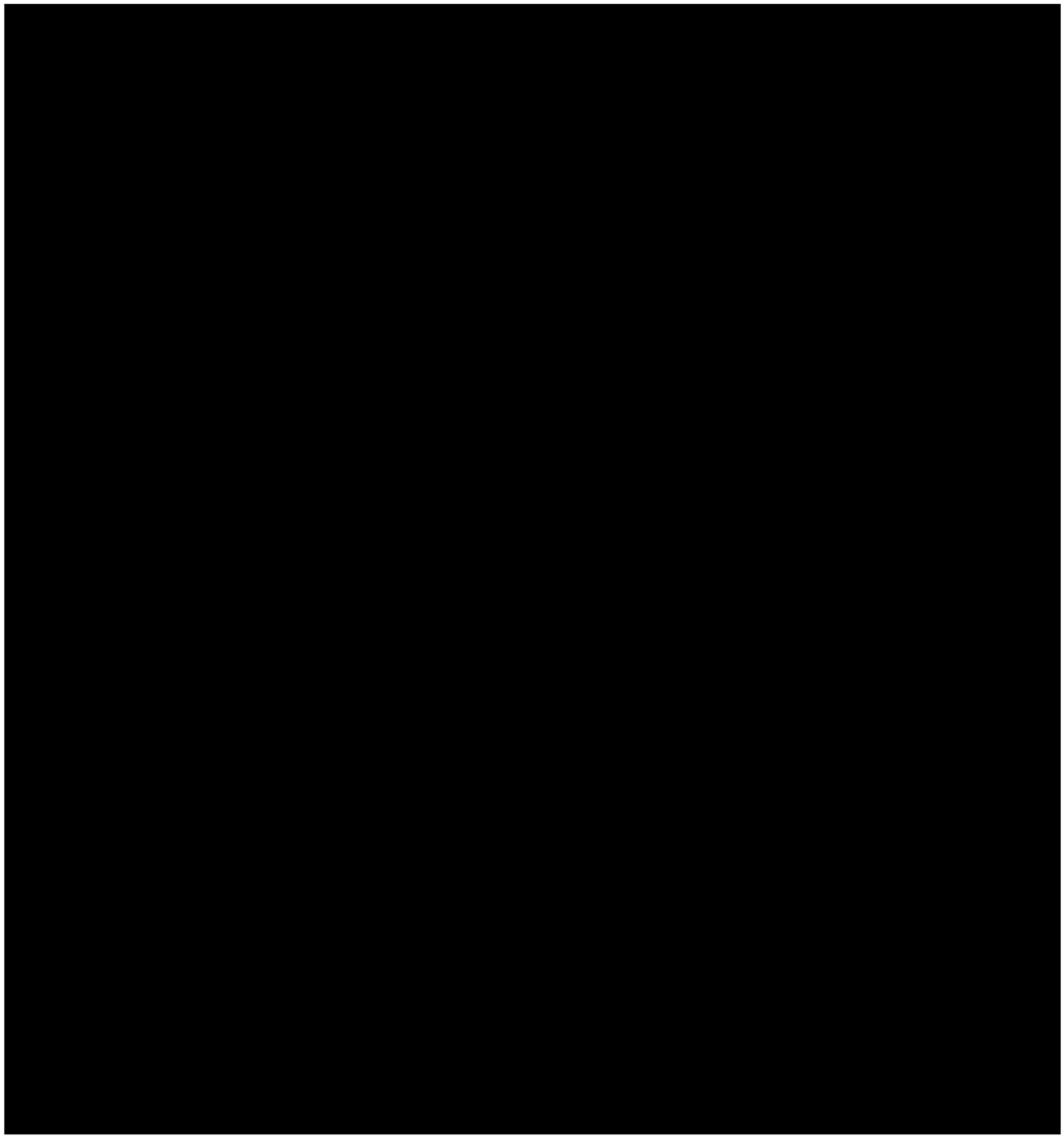
16. STUDY INVESTIGATORS

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

REFERENCES

1. Atkins JL and Butler PE, *Hyperhidrosis: a review of current management.* Plast Reconstr Surg, 2002. **110**(1): p. 222-8.
2. Boni R, *Generalized hyperhidrosis and its systemic treatment.* Curr Probl Dermatol, 2002. **30**: p. 44-47.
3. Adar R, Kurchen A, Zweig A, Mozes M, *Palmar hyperhidrosis and its surgical treatment: a report of 100 cases.* Ann Surg, 1977. **186**: p. 34-41.
4. Heckmann M, *Hyperhidrosis of the axilla.* Curr Probl Dermatol, 2002. **30**: p. 149-155.
5. Groscurth P, *Anatomy of sweat glands.* Curr Probl Dermatol, 2002. **30**: p. 1-9.
6. Hölzle E, *Pathophysiology of sweating.* Curr Probl Dermatol, 2002. **30**: p. 10-22.
7. Naumann M, Hamm H, *Treatment of axillary hyperhidrosis.* Br J Surg, 2002. **89**: p. 259-261.
8. Collin J, Whatling P, *Treating hyperhidrosis. Surgery and botulinum toxin are treatments of choice in severe cases.* BMJ, 2000. **320**: p. 1221-1222.
9. Hölzle E, *Topical pharmacological treatment.* Curr Probl Dermatol, 2002. **30**: p. 30-43.
10. Tögel B, Greve B, Raulin C, *Current therapeutic strategies for hyperhidrosis: a review.* Eur J Dermatol, 2002. **12**: p. 219-223.
11. White JW Jr, *Treatment of primary hyperhidrosis.* Mayo Clin Proc, 1986. **61**: p. 951-956.
12. Stolman LP, *Treatment of hyperhidrosis.* Dermatol Clin, 1998. **16**: p. 863-869.
13. Anliker MD, Kreyden OP, *Tap water iontophoresis.* Curr Probl Dermatol, 2002. **30**: p. 48-56.
14. Altman RS, Schwartz RA, *Emotionally induced hyperhidrosis.* Cutis, 2002. **69**: p. 336-338.
15. Lillis PJ, Colemen W Jr, *Liposuction for treatment of axillary hyperhidrosis.* Dermatol Clin, 1990. **8**: p. 479-482.
16. Hafner J, Beer GM, *Axillary sweat gland excision.* Curr Probl Dermatol, 2002. **30**: p. 57-63.
17. Kennedy JE, Ter Haar GR, Cranston D, *High intensity focused ultrasound: surgery of the future?* Br J Radiol, 2003. **76**(909): p. 590-9.

ATTACHMENT A: HYPERHIDROSIS DISEASE SEVERITY SCALE



ATTACHMENT B: NUMERIC RATING SCALE