ELIRA -1 Trial

Safety and Effectiveness of Transcutaneous Electrical Nerve Stimulation (TENS)-Assisted Weight Loss

Protocol Number: CD-004

Version: 03

Date: September 25, 2017

ELIRA-1:

SAFETY AND EFFECTIVENESS OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)-ASSISTED WEIGHT LOSS

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Protocol Number: CD-004

Study Device: The Elira wearable, patch system

Date of Protocol: Version 3.0; September 25, 2017

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations. The study will be monitored according to standard clinical monitoring procedures and in compliance with Title 21 CFR Part 812.

I have read and agree to abide by the requirements of this protocol.

_____

Principal Investigator Signature Date

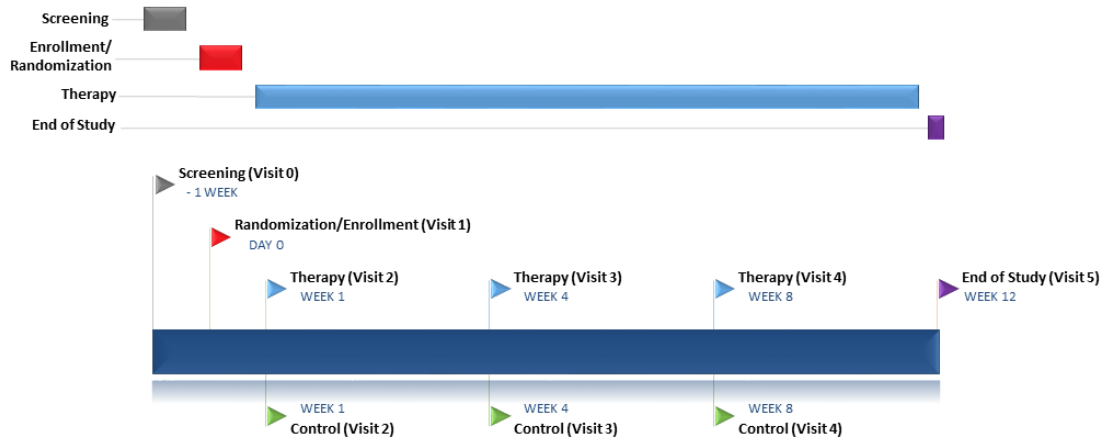
TABLE OF CONTENTS

PROTOCOL SUMMARY

Study Title	Safety and effectiveness of transcutaneous electrical nerve stimulation (TENS) of the T6/T7 dermatome in adult, overweight-to-Type 1 obese- subjects (i.e. BMI of between 25 to 35 kg/m^2 inclusive) when used for weight loss.
Study Coordinating PIs	Shelby Sullivan, MD and Steven Edmundowicz, MD
Study Rationale	Previous studies have shown that TENS facilitates weight loss in overweight subjects. The therapy in these trials was delivered using an over the counter device not optimized for daily use for weight loss. The present pivotal study will test the hypothesis that daily, wearable TENS is safe and effective for weight loss therapy in overweight- to Type 1 obese-subjects (i.e. BMI of 25 -35 kg/m^2 inclusive). Secondarily the study will assess the impact of the TENS therapy on appetite. Ancillary endpoints include changes in hemoglobin A1c, changes in ALT, and blood lipids as secondary measures associated with weight loss.
Name of the Device(s) Used in Study	The Elira wearable, patch system.
Description of Components	The Elira wearable patch system is an RF coupled, wearable transcutaneous electrical nerve stimulation (TENS) device controlled via Bluetooth by a smart phone unit running a custom application which directs therapy from the patch within safe limits set by a clinician and also includes a diary. Subjects will be supplied as well with paper diaries for appetite and symptoms along with an electronic scale.
Study Design	Randomized, adaptive parallel arm study. Subjects will be initially screened during a screening period (+/- 7 days). During this screening period, subjects will sign an Informed Consent Form (ICF), have their weight/height and blood pressure measured, take a pregnancy test (females of child bearing potential), get blood drawn for analysis (CMP, blood lipids, hemoglobin A1c), and complete the PHQ-9 and patient preference survey. At the end of the screening period, eligible subjects will be enrolled/randomized in the study to either a treatment or control group. After enrolling, both control and treatment subjects will be instructed to follow a healthy 1200 calorie diet for the duration of the study and will receive training on the use of the electronic scale and completion of paper diaries. For the treatment group, subjects will be instructed on use of the Elira wearable, patch system. Following this, subjects will enter the Therapy Period for 12-weeks. At the end of the Therapy Period, subjects will complete an end of study visit to be assessed for weight loss, blood pressure, blood lipids, hemoglobin A1c, CMP (Reduction of ALT), patient preference questionnaire and their participation will be considered complete (pending laboratory results, adverse events or serious adverse events). The study utilizes an adaptive approach where cohorts of enrolled/randomized subjects (in groups of 25 per arm) are assessed for dose response and progression to achievement of primary and secondary endpoints. Frequent interim endpoint

	assessment utilizing Markov-chain Monte Carlo (MCMC) methods coupled with Longitudinal analyses will be utilized to determine sample sizes for future cohorts (assessed primarily via Normal dynamic linear modeling [NDLM]).
Subject Population / Sample Size	The primary endpoint is powered at a final enrollment of 75 subjects per group, for a total of 150 subjects, but interim analyses based on Bayesian posterior probability distributions with multiple imputation will be utilized to assess interim significance. In the event the interim analysis is not significant, up to 300 subjects may need to be enrolled in order to achieve final separation between groups for statistical significance. Thus, Elira may need to screen up to 500 subjects to account for exclusions prior to enrollment.
Study Duration and Sites	Minimum study duration for each patient will be 13 weeks. As it is expected that recruitment of 150 subjects will take up to 12 weeks, the overall study duration is anticipated to be a minimum of 26 weeks, assuming all cohorts are enrolled. The study will be conducted at up to 10 centers.
Inclusion Criteria	Subject is between 18 – 65 years of age inclusive. Subject has a BMI of 25-35 kg/ m^2 inclusive. Subject has signed the informed consent form and is able to comply with study protocol and adhere to study visit schedule. Subject is able to wear and use a wearable, patch TENS system. Subject is able to use a touch screen hand held smart phone. Subject is fluent in English and can complete patient questionnaires. Subject can comply with a 1200 calorie diet for the duration of the study. Subject is male or non-pregnant, non-lactating female, who agrees to use effective contraceptive methods throughout the length of the trial based on PI approval. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at screening or enrollment visit, prior to placement of ELIRA device.
Exclusion Criteria	Subject has any known gastrointestinal disorder that in the opinion of the PI precludes enrollment into the trial. Subject has had a prior bariatric procedure or any previous procedure on the stomach. Subject has any significant multisystem disease in the opinion of the PI. Subject has > 6.5 HbA1c. Subject has significant cardiac arrhythmia, ectopy, or significant cardiovascular disease. Subject has an existing implanted electrical stimulator (e.g., pacemaker, AICD). Subject is a female of child-bearing potential who is pregnant or intends to become pregnant during the trial period. Subject has current and/or a history of cancer within the past 5 years (not including basal cell carcinoma or cervical carcinoma in situ). Subject has had a weight change of $\pm$ 5% of his/her Total Body Weight in the 3 months prior to screening.

	Subject has a moderate / severe psychiatric disorder. Subject has a diagnosed neurological disease. Subject has a diagnosed eating disorder. Subject has a skin disorder affecting the thoracic dermatomes. Subject has active or has ever had shingles in the abdominal area. Subject has abdominal surgery or other scars which may interfere with stimulation in the opinion of the PI. Subject is currently enrolled in other, potentially confounding research. Subject has known allergic reaction to materials in the electrodes and/or is otherwise unable to tolerate stimulation with the wearable TENS system. Subject is actively participating or unwilling to discontinue participation in another weight loss program. Subject is taking weight loss control medications including but not limited to OTC medications, Metformin, and Belviq. Subject is unable to take anti-nausea medications planned for the study. Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking). Current smoker or user of nicotine product or smoking cessation within 1 year of the screening date. History of treatment for or current abuse of drugs or alcohol. A score of ≥10 on the Patient Health Questionnaire 9 (PHQ-9), demonstrating moderate depression. Any subject that the investigator considers inappropriate for the study for medical reasons. Subject has a history of moderate/severe migraines or severe headache disorders requiring the treatment of Topiramate. Subject has a history of migraines or severe headache disorders requiring the treatment of Topiramate. Subject is on drug therapy which may alter antral motility or appetite, per PI discretion (Appendix 8).

Study Outline	
Dosing Regime	Treatment subjects will be trained in rotation of the patch electrodes every 24h such that it is applied to varying locations on the T6/T7 dermatome. Each treatment subject will receive up to 30 mA of sustained current stimulation (up to 40mA peak) for 30 minutes after each of three meals per day (delivered within 1-hour post prandially). Based on tolerance of the therapy, a subject may decrease his or her dose by dropping one of the 3 post prandial sessions after receiving approval from a clinical coordinator and/or PI. Subjects who do not experience sufficient appetite suppression may add 15-minute pre-prandial rescue sessions delivered within 2 hours before each meal after receiving approval from a clinical coordinator and/or PI. The nominal stimulation dose per day for any subject will thus be 2400 mA (60 minutes at 40 mA) while the maximum dose for any given subject will be 5400 mA (135 minutes at 40 mA).
Visit Schedule	**Screening/Baseline Visit 0 (-1 week; ± 7 days) –** Obtain Informed Consent prior to any study procedures. Confirm subject has met all inclusion criteria and no exclusion criteria. History & Physical including height & weight, diet history, baseline clinical parameters, provide laboratory requisition, urine pregnancy test for women of childbearing potential (WOCBP), and questionnaires. Initiate subject weekly paper diary with training for weekly completion. Subjects will be instructed to return with their weekly paper diary(ies) at their next scheduled visit. **Enrollment/Randomization Visit 1 (Day 0; ± 7 days) –** Confirm subject continues to meet all inclusion criteria and no exclusion criteria. Assessment of T6/T7 dermatomes, clinical parameters, BP, weight, perform urine pregnancy test for WOCBP if not done at screening, administer TFEQ-R18V2 Questionnaire, assess for adverse events and changes to concomitant medications. Subjects will be randomized based on the blocked randomization algorithm. Treatment and Control subjects will be instructed to follow a healthy 1200 calorie diet throughout the study, an electronic scale with instructions on use will be provided, and a paper diary with training for weekly completion will be provided. Subjects will be instructed to return with their paper diary(ies) at the next scheduled visit. Only the treatment subjects will receive a handheld smartphone with the custom application and an Elira wearable patch system. It is recommended for treatment subjects to utilize an TENS Clean-Cote Skin Wipes and/or alcohol prep pad to maintain a clean application area for the treatment. Treatment subjects will also receive Cetaphil Moisturizing Lotion to be used if any irritation occurs at the treatment site. Subject will

	be instructed to notify site immediately if any irritation occurs. Treatment subjects will stimulate under the supervision of the investigator or coordinator for 30 minutes prior to being discharged with the device. Treatment subjects will be assessed for toleration of the stimulation to further evaluate dose adjustment. Treatment subjects will be discharged with the Elira wearable patch system & Smartphone App and instructions on use. Treatment subjects will be instructed to return with the Elira wearable patch system and smartphone app at their next scheduled visit. **Therapy Phase Visits 2, 3 & 4 (week 1, 4, 8 respectively; ± 7 days) –** Treatment and Control subjects will be assessed for adverse events and changes to concomitant medications. Obtain BP and weight. Administer the TFEQ-R18V2 Questionnaire. Collect and review paper diaries, dispense new paper diaries and review instructions for weekly completion. All subjects will be encouraged to follow a healthy 1200 calorie diet throughout the study. Subjects will be instructed to return with their paper diaries at their next scheduled visit. Treatment subjects will be assessed for any adverse device effects (ADE), T6/T7 dermatome assessment, review and download of diary data, and stimulation adjustment (if needed). Treatment subjects will be discharged with the smartphone application and the Elira wearable patch system and instructions on use. Treatment subjects will be instructed to return with the Elira wearable patch system and smartphone app at their next scheduled visit. **End of Study Visit 5 (week 12; ± 7 days) –** Treatment and Control subjects will be assessed for adverse events and changes to concomitant medications. Physical including weight, BP, requisition for laboratory tests, urine pregnancy test for WOCBP, and completion of questionnaires (PHQ9, TFEQ-R18V2, and Patient Preference Survey). Collect and review paper diaries. Treatment subjects will return the Elira wearable patch system and the smartphone application. Treatment subjects will be assessed for ADEs and have their T6/T7 dermatome area examined.
Study Endpoints	Primary Safety/Tolerability Endpoint: Safety/Tolerability will be assessed by the non-inferiority of incidence of serious adverse events (SAEs), unanticipated SAESs(USAEs), device-related SAEs (DSAEs) and Unanticipated Device Related SAEs (UDAEs) that are associated with the TENS therapy throughout the stimulation and the follow-up period versus historical control (compared with other TENS systems). Safety variables will be tabulated and presented for all subjects including enrolled, but discontinued, subjects. Number of subjects undergoing active stimulation and any reasons for discontinuation of study treatment will be tabulated. Primary Effectiveness Endpoint: The primary efficacy endpoint is the percent reduction in total body weight loss (%TBWL), measured as End Weight – Initial Weight divided by Initial Weight, multiplied by 100, at the end of Therapy period compared to Baseline between Treatment and Control. Secondary Effectiveness Endpoints:

	Number of subjects reporting >5% total body weight loss at the end of Therapy compared to Baseline between Treatment and Control Percent change in appetite scores at the end of Therapy period compared to Baseline between Treatment and Control. Blood pressure, blood lipids, CMP (Reduction in ALT) and HbA1c at the end of Therapy compared to Baseline between Treatment and Control groups. % changes in BMI at the end of Therapy compared to Baseline between Treatment and Control groups <u>Ancillary Endpoints:</u> Changes between the following values: Ease of use/prevalence of use errors associated with the patch unit and dietary application during initial training. Subject preference scores at the end of Therapy compared to Baseline between Treatment and Control groups.
Statistical Analysis	Categorical variables will be summarized by number and percent. Continuous variables will be summarized by total number (N), mean, standard deviation (SD), median, minimum and maximum. Ninety-five percent, 2-sided confidence intervals on estimated means and differences in means between treatment and control groups will be calculated (corrected for multiplicity where needed). Confidence intervals will be similarly computed for proportions and differences between proportions. In addition, propensity score and sensitivity analyses will be utilized to compare adverse events and adverse device effects incidence versus historical control. Wilcoxon signed rank tests, Fisher exact tests, and Pearson Correlations will be utilized to compare changes in baseline variables between varying time points of the study (e.g. Baseline versus Therapy) and to correlate stimulation parameters with endpoint values. Markov-chain Monte Carlo Analyses will be utilized to conduct Bayesian posterior probability distributions with multiple imputations allowed to assess treatment efficacy within and between cohorts. The need for additional endpoints to achieve primary and secondary significance will be determined utilizing longitudinal modeling. Finally, dose response will be modeled and analyzed within and between cohorts to determine optimal therapy dose for stimulation in open label period within and between cohorts using Normal dynamic linear modeling (NDLM) since monotonicity of the response cannot be assumed.
Risk/Benefit Analysis	If shown to be safe and effective, the therapy could eventually provide overweight/ moderately obese subjects a low risk option for weight control beyond diet and lifestyle modification alone. The potential adverse events and adverse device effects and risks associated with this study and the use of the patch System are identical to those normally associated with standard TENS system used for pain control and similar indications.

CONTACT LIST

Study Sponsor	ELIRA, Inc.
Coordinating Principal Investigators	Shelby Sullivan, MD and Steven Edmundowicz, MD
Study Monitor	Stephanie Amlung, PhD
Data Management	Danielle Gherardini, RN BSN
Statistical Analysis	Ian Welsford, PhD
Data Safety Monitoring Board	Virender K. Sharma, MD

1. INTRODUCTION

1.1 BACKGROUND

According to the Centers for Disease Control (CDC) up to 35% of adults over the age of 20 are obese, meaning they have a body mass index (BMI) of over 30 kg/m^2 while up to 69% of similarly aged adults are overweight, meaning they have a BMI of 25-30 kg/ m^2 ([1]; Appendix 1). Individuals who are overweight or obese are at high risk for adverse impacts to quality of life (QOL) factors including general health ([2]), pain ([3]) and psychosocial status ([4]). However, losing weight via calorie restriction dieting is notoriously difficult for such individuals ([2]). Sustained loss of even 5-10% of weight is uncommon with most dieters ([2, 3]) with most regaining nearly half of the lost weight after one year ([4]). While the precise physiological, sociological and genetic factors associated with weight gain and weight loss remain an area of intense investigation, what is becoming clear is that sustained weight loss requires long term calorie intake reduction ([2]), which, in turn, appears to require, among other factors, appetite control ([2, 4]). The purpose of the present non-significant risk (NSR) study is to investigate the effect of transcutaneous electrical nerve stimulation (TENS) on weight loss in overweight-to moderately (i.e. Type 1) obese individuals (i.e. BMI of 25 to 35 kg/ m^2 inclusive [15,16]; Appendix 1) with a long-term goal of determining if such an approach may be of benefit in assisting such individuals in achieving their weight loss goals.

1.2 PENS AND TENS FOR WEIGHT LOSS

Transcutaneous electrical nerve stimulation (TENS) involving the delivery of electrical current to subcutaneous nerve branches via an electrode placed on the skin surface is a well-established treatment modality for muscle pain, muscle atrophy and spasms as well as for pain associated with a variety of conditions including diabetic neuropathy. More recently this modality has been shown to be effective in treating certain symptoms associated with migraine headaches by delivering electrical stimulation to branches of the trigeminal nerve ([8]). A related therapy, Percutaneous Electrical Nerve Stimulation (PENS), in which electrode is inserted into the epidermis, is now in general medical usage for the treatment of urinary incontinence, fecal incontinence, and back pain ([5-8]).

The clinical evidence for a PENS effect on appetite and weight loss is provided by Ruiz-Tovar's study which demonstrated significant weight loss for PENS stimulation of dermatome T6 (the area of skin supplied by cutaneous branches of a single cranial or spinal nerve) via appetite suppression in a European sham control study of 105 subjects ([9]). Similar preliminary clinical results utilizing TENS have been reported in appetite control and subsequent weight loss by Dr. John Faul, a Stanford University researcher, who was granted a method patent (Transcutaneous Electrical Nerve Stimulator for Appetite Control) for his invention that uses TENS to stimulate the thoracic spine area at T6–T10. Each of these studies utilized obese subjects and provided stimulation only during in-clinic supervised sessions. The present study is designed to extend these preliminary studies by utilizing TENS in overweight-to Type 1 obese-subjects (i.e. BMI of between 25 and 35 kg/ m^2 inclusive [15,16]) stimulating in an outpatient/at home setting using a wearable, patch TENS system.

1.3 THE HYPOTHESIZED MECHANISM OF T6/T7 STIMULATION FOR APPETITE SUPPRESSION AND WEIGHT LOSS

The effect of PENS, and presumably, TENS, has been widely demonstrated by posterior tibial nerve neurostimulation in treating urinary and fecal incontinence, creating a somato-autonomic reflex ([10,11]; Figure 1). The definition of a somato-autonomic reflex is a reflex elicited by stimulation of somatic tissue (strictly speaking, tissue of the musculoskeletal system and the dermis of the skin), and manifesting as an alteration of the autonomic nervous

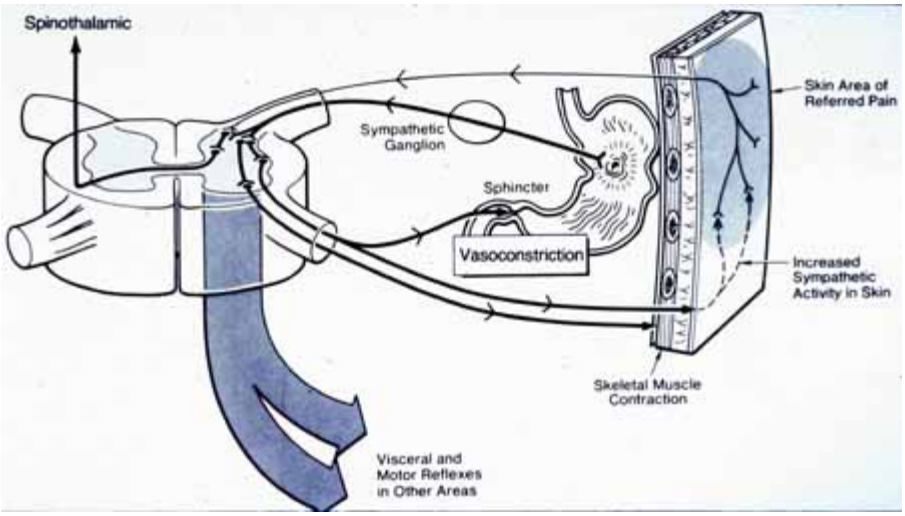


Figure 1: Somato-Autonomic Reflex Arc

system function (Figure 1). Altered autonomic nervous system functions may lead to changes in the function of dependent organs (like the stomach and other gastrointestinal organs), a situation sometimes referred to as a Somato-visceral reflex. To the PI's knowledge, the study cited by Ruiz-Tovar is the first to report using PENS of dermatome T6 to reduce appetite and, consequently, obtain a clinically-significant weight loss ([9]). It is likely that the effect is produced by the creation of a Somato-autonomic reflex in similar fashion to percutaneous electrical stimulation of the posterior tibial nerve in treating incontinence, but in this case suppressing appetite ([10]).

As supported by Dr. Faul's preliminary results ([9]), it is likely that similar results to PENS can be obtained using TENS to stimulate the same region, given the shallow 2 to 4 millimeter depth of sensory afferents throughout the target dermatome. Chen reported that electric gastric stimulation with a gastric pacemaker may affect the central nervous system by segregating hormones in the stomach and regulating satiety and/or appetite, with ghrelin being particularly involved in this mechanism ([11]). As shown by Ruiz-Tovar's study, the electric stimulation's main effect is appetite reduction. This study consisted of 105 subjects divided into 3 groups. Group 1 included 45 subjects who underwent dermatome T6 stimulation and maintained a 1,200 calorie diet and who were scheduled for bariatric surgery. These subjects had BMIs of greater than 40 or greater than 35 with co-morbidities. Group 2 included 45 subjects that maintained a 1,200 calorie diet only and who were scheduled for bariatric surgery. These subjects also had BMIs of greater than 40 or greater than 35 with co-morbidities. Group 3 included 15 subjects with a BMI greater than 30 who received sham stimulation (at the ankle) and who maintained a 1,200 calorie diet. Group 1, the treatment arm, evidenced dietary compliance in excess of 90% and achieved a significant weight loss success (equal to or greater than 5 kilograms (11 pounds) in 76.7% of subjects, as compared to Groups 2 and 3 where weight loss success was less than 6.7% and 0.0%, respectively. No complications were observed associated with the technique.

It thus appears likely that, through safely stimulating T6/T7 via TENS, a Somato-visceral reflex arc will be activated which will suppress appetite and support eventual weight loss in overweight and obese subjects.

2. STUDY RATIONALE

The purpose of the present study is to determine the safety and effectiveness of stimulation via a wearable patch TENS system of the T6/T7 dermatome on appetite suppression in adult (18 to

65 years of age inclusive), overweight/obese subjects (i.e. a BMI of 25 to 35 kg/m^2 inclusive[15, 16]; Appendix 1) who desire to lose weight. The study will seek thus to extend existing data on the use of dermatomal stimulation on obese and morbidly obese patient to subjects who are overweight/obese (i.e. a BMI of 25 to 35 kg/m^2 [15, 16]; Appendix 1).

2.1 JUSTIFICATION FOR STUDY GIVEN RISK/BENEFIT OUTCOME

Up to 35% of adults over the age of 20 in the United States are overweight. Being overweight places individuals at higher risk for a number of what are termed metabolic disorders including diabetes mellitus. This risk association is thought to be the reason for the high health care costs associated with overweight and obesity. While diet and exercise do show efficacy in a substantial subset of subjects, long term weight control is difficult to achieve for the vast majority of overweight individuals. The physiological and psycho-social reasons for this are not well characterized and likely highly complex, but a key component of this challenge is associated with appetite control. The present study seeks to determine if a method of appetite control utilizing T6/T7 dermatome stimulation in obese individuals can be utilized to the broader overweight population. The study utilizes non-invasive TENS stimulation within the range of the energy delivery well known to be safe for at-home use for nerve and muscle pain. Subjects will be informed of all potential side effects related to stimulation prior to enrollment and, throughout the study, subjects will be monitored and allowed to decrease or discontinue stimulus if any such side effects are deemed to be intolerable for participants.

In addition, since appetite and weight loss can be affected by a variety of physiological and psychosocial factors ([12,13, 15, 17]), the change in appetite will be measured weekly using a validated tool, the Visual Analog Scale (VAS[14]; See Appendix 3**)** and also assessed at baseline at the end of the study via administration of the Three Factor Eating Questionnaire R-18 V2 (TFEQ-R1V2[17, 18]). Please note that while the VAS was first developed for pain, it has been validated for weight loss/appetite applications ([14]) while the TFEQ-R18V2 has specifically been validated in weight loss applications ([17, 18]). The present study is not intended to be a formal validation of the assessment tool's applicability to the population targeted by the present study per se; it is intended simply as an assessment of potential changes in such parameters correlated with delivery of therapy during the study. Thus, the use of the tool as presented is considered scientifically valid.

Thus, the non-significant risk of the study is more than balanced by the potential societal benefit of the development of this novel, non-invasive appetite control method.

3. DEVICE DESCRIPTION

The TENS System consists of:

TENS Unit (Appendix 2)	ELIRA wearable Patch
Electronic Diary tool (Appendix 5)	Diary/dietary application running on and Android Smart-phone: 4.5" 720p HD TFT display Size (LWH): 2.6 inches, 0.46 inches, 5.1 inches Weight: 4.96 ounces
Device Accessories	Extra packs ELIRA electrodes Device/Phone Chargers Electronic Scale Plastic Phone Cover and System Pack

Other study accessories	TENS Clean-Cote Skin Wipes, **ALCOHOL** prep pads, Cetaphil Moisturizing Lotion

4. STUDY OBJECTIVES

The objectives of this study are to demonstrate safety and effectiveness of a wearable patch TENS system (Appendix 2) in driving weight loss when coupled with an integrated weight loss reduction strategy. The study is designed to demonstrate that TENS stimulation sufficient to drive weight loss is safe and tolerable when compared to standard of care, and that adverse events/adverse device effects are similar to other TENS device use cases.

5. STUDY DESIGN

Randomized, adaptive parallel arm study. Subjects will be initially screened during a screening period (1 week, ±7 days; Figure 2). During this screening period, prior to study procedures being performed, subjects will sign an informed consent form. Then they will have their

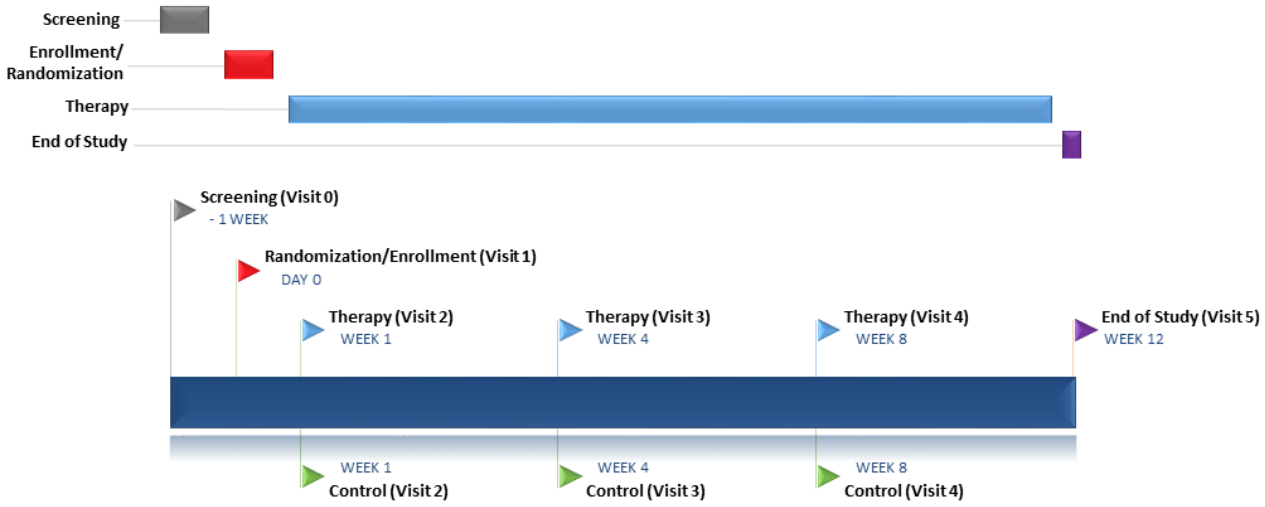


Figure 2: Study Outline

weight and blood pressure measured, FOCBP will have a pregnancy test, get blood drawn for analysis (blood lipids, CMP, hemoglobin A1c), and complete patient preference questionnaires. At the end of the screening/baseline period, eligible subjects will be offered the chance to enroll in the study. After enrolling, subjects will be randomized to treatment or control groups.

The Treatment group will be instructed to follow a healthy 1200 calorie diet that they will follow for the duration of the study and will receive training on the use of the weekly paper diary, electronic scale, smartphone app and the Elira wearable patch system. All treatment subjects will be required to stimulate in the office for a period of time to confirm sufficient system training and tolerability of the stimulation. Following this, subjects will enter the Therapy Period, for a 12-week duration.

The Control group will be instructed to follow a healthy 1200 calorie diet that they will follow for the duration of the study and will receive training on the use of the weekly paper diary and electronic scale. The Control group will not receive the electronic smartphone app or the Elira wearable patch system.

At the end of the Therapy Period, subjects will be assessed for weight loss, blood pressure, CMP, blood lipids, HbA1c, and will be terminated from the study.

The study utilizes an adaptive approach where cohorts of enrolled subjects (in groups of 25 per arm) are assessed for dose response and progression to achievement of primary and secondary endpoints. Frequent interim endpoint assessment utilizing Markov-chain Monte Carlo (MCMC) methods coupled with longitudinal analyses will be utilized to determine sample sizes for future cohorts (assessed primarily via Normal dynamic linear modeling [NDLM]).

5.1 DOSING SCHEDULE

All Treatment Subjects will be trained in rotation of the patch electrodes every 24h such that it is applied to varying locations on the T6/T7 dermatome. Each active therapy subject will receive up to 30 mA sustained current of stimulation (up to 40mA peak) for 30 minutes after each of three meals per day (delivered within 1-hour post prandially). Based on tolerance of the therapy, a subject may decrease his or her dose by dropping one of the 3 post prandial sessions after receiving approval from a clinical coordinator and/or PI. Subjects who do not experience sufficient appetite suppression may add up to three 15-minute pre-prandial rescue sessions delivered within 2 hours before each meal after receiving approval from a clinical coordinator and/or PI. The nominal stimulation dose per day for any subject will thus be 2400 mA (60 minutes at 40 mA) while the maximum dose for any given subject will be 5400 mA (135 minutes at 40 mA).

During the therapy period, Treatment Subjects will undergo initial assessments to ensure they are familiar with the device, the daily electronic diary, weekly paper diary, and the 1200 calorie diet. All subjects (Treatment and Control) will be required to undergo follow-up assessments at least once per every 4 weeks during the study. Up to two additional unscheduled visits per subject will be permitted during the study. PI will oversee any adjustments to treatment dosing or stimulation parameters.

5.2 DATA COLLECTION:

All subjects will be asked to keep a VAS paper diary (hunger, appetite, well-being) in which they will record such values weekly. Subjects will record their diary variables. For treatment subjects, any adjustments to stimulation session schedule will be recorded within the electronic diary and by clinical coordinators.

5.3 ASSIGNMENT & BLINDING

Subjects meeting the Inclusion and Exclusion criteria will be enrolled and randomized into either Treatment or Control groups. The randomization algorithm will be blocked to account for site bias and to ensure counterbalance across sites. As this is an open label study, there will be no consideration for blinding.

6. STUDY ENDPOINTS

6.1 PRIMARY ENDPOINTS

6.1.1 Primary Safety/ Tolerability Endpoints:

- Safety/Tolerability will be assessed by the non-inferiority of incidence of serious adverse events (SAEs), unanticipated SAES (USAEs), device-related SAEs (DSAEs) and Unanticipated Device Related SAEs (UDAEs) that are associated with the TENS therapy throughout the therapy/treatment period versus historical control.
- Safety variables will be tabulated and presented for all subjects including enrolled, but discontinued, subjects. Number of subjects undergoing TENS and any reasons for discontinuation of study treatment will be tabulated.

6.1.2 Primary Effectiveness Endpoint:

The primary effectiveness endpoint is the percent reduction in total body weight loss (%TBWL), measured as End Weight – Initial Weight divided by Initial Weight, multiplied by 100, at the end of Therapy period compared to Baseline between Treatment and Control.

6.1.3 Secondary Effectiveness Endpoints:

- Number of subjects reporting >5% total body weight loss at the end of Therapy as compared to Baseline between Treatment and Control
- Percent change in appetite scores at the end of Therapy Period compared to Baseline between Treatment and Control.
- Blood pressure, blood lipids, ALT and HbA1c at the end of Therapy Period as compared to Baseline between Treatment and Control groups.
- % changes in BMI at the end of Therapy Period compared to Baseline between Treatment and Control groups

6.1.4 Ancillary Endpoints:

Changes between the following values:

- Ease of use/prevalence of use errors associated with the patch unit and dietary application during initial training.
- Subject preference scores at the end of Therapy Period compared to Baseline between Treatment and Control groups.

6.2 ENDPOINT DEFINITIONS & RECORDING METHODS

Endpoint data in hunger, appetite, and dietary compliance are obtained from subject reported assessments (Appendix 4, 5). That is, the measurement of success is based on the subject's report of the parameter using validated tools where available.

Primary source data will be paper based, with each subject receiving diary worksheets to record responses. Treatment subjects will also be assigned an Android Smart Phone onto which has been loaded a copy of custom dietary application (Appendix 5). Subjects will be trained on the use of these tools and assessed for accurate use prior to taking them home. To ensure data privacy, the network interface card (i.e. SIM card) for the phone will be removed such that data can only be downloaded *via* a direct USB link.

7. STUDY POPULATION

7.1 INCLUSION CRITERIA

7.1.1 Subject is between 18 – 65 years of age inclusive.

7.1.2 Subject has a BMI of 25-35 kg/ m^2 inclusive.

7.1.3 Subject has signed the informed consent form and is able to comply with study protocol and adhere to study visit schedule.

7.1.4 Subject is able to wear and use a wearable, patch TENS system.

7.1.5 Subject is able to use a touch screen hand held smart phone.

7.1.6 Subject is fluent in English and can complete questionnaires.

7.1.7 Subject can comply with a 1200 calorie diet for the duration of the study.

7.1.8 Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at screening or enrollment visit, prior to placement of ELIRA device.

7.1.9 Subject is male or non-pregnant, non-lactating female, who agrees to use effective contraceptive methods throughout the length of the trial based on PI approval.

7.2 EXCLUSION CRITERIA

7.2.1 Subject has any known gastrointestinal disorder that in the opinion of the PI precludes enrollment into the trial.

7.2.2 Subject has had a prior bariatric procedure or any previous procedure on the stomach.

7.2.3 Subject has any significant multisystem disease in the opinion of the PI.

7.2.4 Subject has > 6.5 HbA1c.

7.2.5 Subject has significant cardiac arrhythmia, ectopy, or significant cardiovascular disease.

7.2.6 Subject has an existing implanted electrical stimulator (e.g., pacemaker, AICD).

7.2.7 Subject is a female of child-bearing potential who is pregnant or intends to become pregnant during the trial period.

7.2.8 Subject has current and/or a history of cancer within the past 5 years (not including basal cell carcinoma or cervical carcinoma in situ).

7.2.9 Subject has had a weight change of $\pm$ 5% of his/her Total Body Weight in the 3 months prior to screening.

7.2.10 Subject has a moderate / severe psychiatric disorder.

7.2.11 Subject has a diagnosed neurological disease.

7.2.12 Subject has a diagnosed eating disorder.

7.2.13 Subject has a skin disorder affecting the thoracic dermatomes.

7.2.14 Subject has active or has ever had shingles in the abdominal area.

7.2.15 Subject has abdominal surgery or other scars which may interfere with TENS stimulation in the opinion of the PI.

7.2.16 Subject is currently enrolled in other potentially confounding research.

7.2.17 Subject has known allergic reaction to materials in the TENS electrodes and/or is otherwise unable to tolerate stimulation with the wearable TENS system.

7.2.18 Subject is actively participating or unwilling to discontinue participation in another weight loss program.

7.2.19 Subject is taking weight loss control medications including but not limited to OTC medications, Metformin, and Belviq.

7.2.20 Subject is unable to take anti-nausea medications planned for the study.

7.2.21 Inability to walk at least 0.8 kilometers per day (10 minutes of continuous walking).

7.2.22 Current smoker or user of nicotine product or smoking cessation within 1 year of the screening date.

7.2.23 History of treatment for or current abuse of drug or alcohol.

7.2.24 A score of ≥10 on the Patient Health Questionnaire 9 (PHQ-9), demonstrating moderate depression.

7.2.25 Any subject that the investigator considers inappropriate for the study for medical reasons.

7.2.26 Subject has a history of moderate/severe migraines or severe headache disorders requiring the treatment of Topiramate.

7.2.27 Subject is on drug therapy which may alter antral motility or appetite, per PI discretion. (Appendix 8)

7.3 SELECTION AND ENROLLMENT OF SUBJECTS

Prospective study subjects will be screened for study eligibility. A subject is considered enrolled after:

1. Written Informed Consent is obtained.
2. Meeting all inclusion and exclusion criteria and randomized into the study.
3. This study will utilize unique subject numbers for the purpose of trial data collection. Subjects signing an Informed Consent but not meeting all criteria will not be considered enrolled in the study but the signed Informed Consents will be maintained by the PI for seven (7) years.

Following enrollment, subjects should remain in the study until completion of the required Therapy Phase.

A subject's participation may be discontinued for the following reasons:

- Subject Withdrawal: As subject participation in a clinical trial is voluntary, the subject may choose to discontinue participation at any time without penalty or loss of benefits.
- Investigator Termination: The Investigator may terminate the subject's participation without regard to the subject's consent if the Investigator believes termination is medically necessary.
- Lost-to-Follow-up: A subject is lost-to-follow up if he/she does not complete required follow-up, but has not "officially" withdrawn consent. In order to consider a subject lost to follow-up, site personnel should make all reasonable efforts to locate and communicate with the subject. A minimum of three (3) attempts to contact the subject should be recorded in the source documentation including date, time and name of site personnel attempting to make contact.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Categorical variables will be summarized by number and percent. Continuous variables will be summarized by total number (N), mean, standard deviation (SD), median, minimum and maximum. Ninety-five percent, 2-sided confidence intervals on estimated means and differences in means between treatment and control groups will be calculated. Confidence intervals will be similarly computed for proportions and differences between proportions. In addition, propensity score and sensitivity analyses will be utilized to compare adverse events and/or adverse device effects incidence versus historical control. Wilcoxon signed rank tests, Fisher exact tests, and Pearson Correlations will be utilized to compare changes in baseline variables between varying

time points of the study (e.g. baseline versus post stimulation treatment) and to correlate stimulation parameters with endpoint values. Markov-chain Monte Carlo Analyses will be utilized to conduct Bayesian posterior probability distributions with multiple imputations allowed to assess treatment efficacy within and between cohorts. The need for additional endpoints to achieve primary and secondary significance will be determined utilizing longitudinal modeling. Finally, dose response will be modeled and analyzed within and between cohorts to determine optimal therapy dose for stimulation in open label period within and between cohorts using Normal dynamic linear modeling (NDLM) since monotonicity of the response cannot be assumed.

8.1.1 Safety/Tolerability

The primary safety endpoint is defined as the proportion of subjects free of TENS - related serious adverse events and/or adverse device effects through the therapy phase (safety success rate). The AE and/or ADE rates will be summarized utilizing descriptive statistics and compared utilizing parametric and non-parametric methods as deemed appropriate. The null and alternative hypotheses are:

H_0: $\pi_T \leq \pi_C$

H_1: $\pi_T > \pi_{C,}$

Where π_T and π_C are the probabilities of adverse events and/or adverse device effects in treatment versus historical control respectively.

8.1.2 Appetite Suppression

The null and alternative hypotheses are:

H_0: $\pi_T \leq \pi_C$

H_1: $\pi_T > \pi_{C,}$

Where π_T and π_C are the probabilities of appetite suppression in treatment versus control respectively. Pearson correlation will be utilized to correlate appetite score (as measured with TFEQ-18V2; [17, 18]) with stimulation dose. Estimates of 95% confidence intervals will also be computed for the difference between varying levels of stimulation. Wilcoxon signed rank tests and/or Kruskal Wallis statistics will be utilized to make comparisons between groups as required. Estimates and 95% confidence intervals will also be computed for the difference in appetite levels between Baseline and Therapy Periods.

8.1.3 Weight Loss

The null and alternative hypotheses are:

H_0: $\pi_T \leq \pi_C$

H_1: $\pi_T > \pi_{C,}$

Where π_T and π_C are the probabilities of weight loss (% TBWL, %EBWL) in treatment versus control respectively. Estimates of the proportion of weight loss in pounds, % total body weight loss (%TBWL) Excess Body Weight Loss (%EBWL) or BMI will be compared with a tested Fishers Exact Test. Estimates and 95% confidence intervals will also be computed for the difference in rate of weight loss between varying stimulation levels.

8.2 JUSTIFICATION OF SAMPLE SIZE

The calculated sample size for the study is based on conservative imputation of results from other studies on weight loss including the use of TENS for weight loss. The degree of coaching/dietary support throughout the present study is moderate intensity lifestyle/weight coaching. The sample size modeling assumes an average of 3.5% TBWL in Control subjects using diet and exercise alone. The estimated weight loss in the Treatment subjects is modeled from preliminary data on T6/T7 dermatomal TENS when used for weight loss: 7.5% TBWL. The variance of the responses in the study (i.e. Standard Deviation) was modeled at ± 5% TBWL. This value was taken from previous dermatomal TENS weight loss study results. The model assumes a 30% drop out rate across groups and an 80% powered endpoint using an adaptive p spending model wherein interim posterior probability assessments are allowed after enrolling proscribe cohorts of not less than 25 subjects per group for not less than 7 weeks of stimulation. The alpha penalty will be minimized per interim by assessing the relationship between stimulation (i.e. dose) and weight loss using Normalized Linear Dynamic Modeling (NLDM) to determine overall sample size projected (i.e. futility) rather than assessing the primary endpoint hypothesis per se. Monotonicity will not be assumed in this analysis. This modeling provides an estimate of 75 subjects per group, for a total study size of 150 subjects. However, the protocol allows for enrollment of additional subjects should the interim model project under powering of the primary endpoint.

8.3 RETENTION AND HANDLING OF MISSING DATA

Every effort will be made to collect all data at each time point in the study. The PI and the Clinical Data Monitor will minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of subjects, and training of clinicians. If a subject misses a dietary entry into either the paper or electronic diary, a look back entry for that value is allowed provide for the week preceding the event. Outside this window, data will be considered missing. All partial data available for subjects who drop out during the course of the study will be included.

For missing data imputation, the last value carried forward method will be utilized. To assess the potential effect of missing data on the primary effectiveness endpoint, the following sensitivity analyses will be performed to impute missing values.

Sensitivity Analyses: First, the primary effectiveness endpoint will be assessed with all missing data points imputed as failures for both groups. Second, the primary efficacy endpoint will be assessed with all missing data points imputed as successes for both groups.

8.4 SUBJECT POPULATION FOR SAFETY AND EFFECTIVENESS ANALYSIS

Safety analyses will be conducted an Intent to Treat (ITT) basis (i.e. all subjects who were enrolled). Primary and Secondary effectiveness analyses will be performed on a modified intent-to-treat basis (MITT; i.e. all subjects who initiated therapy, defined as subjects who initiated their first Treatment Period Visit) as will all per subject effectiveness analyses (e.g. responder analyses). Primary and Secondary endpoints (e.g. weight loss, appetite) will also be conducted on a completer, or per protocol basis (defined as those subjects that completed all visits in the study).

8.5 DEVIATIONS FROM THE STATISTICAL ANALYSIS PLAN

Any deviations in the analysis of the final data set from the statistical analysis plan will be documented and justified in the final report.

9. STUDY PROCEDURES

The study is divided into four phases as defined below (See Appendix 6 for Schedule of Visits):

Study Phase	Definition
Screening/Baseline Visit	Obtain Informed Consent. Completion of Patient Preference Survey. Determination of Inclusion and Exclusion criteria (including PHQ-9 questionnaire; Appendix 3), Medical History and Physical, Assessment of T6/T7 Dermatomes, Obtain Concomitant Medications, Weight Loss History, Blood Pressure, Height and Weight, Blood Tests (including a lipid panel, HbA1c and CMP), and Urine Pregnancy Test for WOCBP. Dispense and Instruct on completion of Weekly Diary.
Randomization / Enrollment Visit	Confirm Inclusion/Exclusion criteria has been met, Weight, blood pressure, and AEs/Concomitant Medications assessed. Completion of baseline TFEQ-R18V2 (Appendix 4). Assessment of T6/T7 Dermatomes, UPT for WOCBP (if not done at screening), Randomization of subject. For both groups (control and treatment) train and dispense weekly paper diaries and electronic scale, encourage 1200 calorie diet for duration of study. In Addition, For Treatment Group only, training and assessment of use of smart phone app and Elira wearable patch system (Appendix 2); Initiation of therapy and dose adjustment. Provide TENS Clean-Cote Skin Wipes and/or Alcohol Prep Pads and Cetaphil Moisturizing Lotion with instructions on use as needed, dispense smart phone app and Elira wearable patch system.
Therapy Period	For Control and Treatment Groups: collect and review weekly paper diary (dispense additional diaries), weight, blood pressure, assess for AE's/concomitant medications, completion of TFEQ-R18V2, encourage continuation of 1200 calorie diet at each scheduled visit. In Addition, For Treatment Group only: assess for Adverse Device Effects at each visit. Collect Elira wearable patch system and smart phone and download data, assess subjects use of electronic diary completion and stimulation sessions at each visit. Dispense smart phone app and Elira wearable patch system at each visit.
End of Study Visit	For Control and Treatment Groups: Collect and review the weekly paper diary, Physical, weight, determine BMI, blood pressure, assess for AE's/concomitant medications, UPT for WOCBP, completion of PHQ9, TFEQ-R18V2, Patient Preference Survey, Blood Tests (including a lipid panel, HbA1c and CMP). In Addition, For Treatment Group only: assess for Adverse Device Effects, collect Elira Wearable patch system and smart phone and download data, assess subjects use of electronic diary completion and stimulation sessions. Assess T6/T7 dermatomes.

9.1 INFORMED CONSENT

Prior to subject participation in this study, the PI or designee must obtain written Institutional Review Board (IRB) approval for the protocol and the Informed Consent Form.

Once the subject's eligibility has been determined, the Investigator or person designated by the Investigator who has been trained to the Protocol, will explain the nature and scope of the study, discuss potential risks and benefits of participation, answer all questions from the subject and ask the subject to participate in the study. The study will be explained to the study subject in lay terms. If the subject agrees to participate, the Informed Consent must be personally signed and dated by the subject and the Investigator or person designated by the Investigator. Any additional persons required to sign the Informed Consent by the IRB will also do so. A copy of the signed and dated Informed Consent must be provided to the study subject. Study subjects will be assured that they may withdraw from the study at any time and for any reason.

Failure to obtain a signed Informed Consent prior to the procedure constitutes a major Protocol deviation.

9.2 SCREENING PROCEDURES

All candidates must be screened for eligibility. A member of the research team assigned to the study should review the subject's medical history to screen for eligibility.

The following tests and procedures must be performed prior to TENS therapy:

- Physical examination, medication history, height, weight and BMI.
- Relevant medical history including subject demographic information and weight loss history.
- Patient Preference Survey and PHQ-9.
- Urine Pregnancy Test (UPT) for WOCBP; blood lipid panel, CMP and HbA1c.

9.3 PHYSICAL EXAMINATIONS

A general physical examination will be performed as well as an examination of organ systems (central nervous system [CNS], cardiac, peripheral vascular, pulmonary, musculoskeletal, abdominal, dermatologic and lymphatic). The dermatologic exam will focus on Dermatome T6-T7 site for any active disease, scars, tattoos, or other problems that would make the site unacceptable for the TENS Unit. Depilation by waxing, shaving, chemical depilatories or any other method in the selected application site is not allowed during the study.

9.4 BODY MASS INDEX

Height and weight without shoes will be used to determine body mass index (BMI) in accordance with the BMI Chart ([15,16];Appendix 1) and confirmed by NIH BMI Calculator. Subjects will be encouraged to wear the same or similar clothing at each visit for more consistent weight measurements.

9.5 MEDICAL HISTORY AND DEMOGRAPHICS

A complete medical history evaluation, including surgical history and demographic data (age, gender, race, ethnicity, and highest level of education) and weight loss history will be obtained for each subject.

9.6 VITAL SIGNS

Blood Pressure (sitting position after 3 minutes rest) will be measured.

9.7 MEDICATIONS

All medications must be reported on the appropriate case report form (CRF) through the end of study. Medications must remain stable from Screening/Baseline through the Therapy Phase of the study. The only exception is medications may be changed for subject health or safety reasons (but not specifically to attempt to reduce weight loss or appetite).

9.8 QUESTIONNAIRES

All subjects will be required to complete the Patient Preference Survey and PHQ-9 at screening/baseline visit. All subjects will be required to complete a weekly VAS diary for hunger and appetite from screening/baseline until completion of the study. All subjects will be required to complete the TFEQ-R18V2 at enrollment and at each Therapy Visit (Appendix 3). All subjects will be required to complete PHQ-9, TFEQ-R18V2, and Patient Preference Survey at the last study visit (Visit 5 or early termination visit).

9.9 URINE PREGNANCY TESTS (UPT)

A urine pregnancy test will be done in the clinic for all females of child-bearing potential (FOCBP) prior to enrollment in the study. The results will be recorded. This can be completed either at Screening Visit (Visit 0) or Randomization/Enrollment Visit (Visit 1).

9.10 DIET

Subjects will be encouraged to maintain a healthy 1200 calorie diet throughout the study. The study doctor and/or research coordinator will provide guidance to assist the subjects on maintaining the diet.

9.11 ELECTRONIC DAILY DIARY DEVICE

For Treatment Group Subjects only, an Android Smart Phone running a semi-custom daily diary application to capture hunger, calories, and weight will be provided. Subjects will be instructed on use by PI or designee.

9.12 STIMULATION

Refer to the Programming Manual provided with the TENS System for full details on the use of the System (Appendix 2). The subject should be instructed to bring their diary (Appendix 5) to the Investigator's office for all office visits to allow for proper downloading of data.

9.12.1 General information on Stimulation:

The TENS unit utilizes low intensity electrical stimulation to activate nerve endings under the skin. While response to TENS varies typically subjects report a mild tingling or burning sensation during and immediately after stimulation session. In addition, mild numbness, termed paresthesia, may be experienced.

9.12.2 Starting the Therapy Phase

During the Therapy Phase, the subject's TENS is programmed to the following settings:

Parameter	Suggested Initial Setting
Frequency	30 Hz
Pulse-Width	200μs
Amplitude	Up to 30 mA sustained (up to 40mA peak)

It is also important that the subject complete the diary during this period. If subject does not feel sensation, subject is to notify PI or Coordinator because it may indicate improper device function. The TENS unit will be replaced if dropped or becomes defective and non-functioning. It is recommended that subjects confirm response to stimulation during the office visits.

10. RISK ANALYSIS

A detailed description of the potential risks associated with specific aspects of the TENS System and diary use are detailed below:

10.1 RISKS

10.1.1 Application and post application risks

While the TENS unit utilized in the present study delivers therapy in a comparable manner to standard commercially available TENS units, there are some risks associated with the device. These include skin irritation at the site of electrode application, numbness and tingling, pain and burning sensations at the site of stimulation. In addition, there is some chance that subjects may feel some gastrointestinal (GI) symptoms including nausea or other GI discomfort (heartburn, dyspepsia, cramping). Dropping the unit may cause damage to the TENS unit. Subjects are instructed to avoid use of the device if it has been damaged in any way and not to use the device while it or any portion of the subject are immersed in water. Subjects are instructed to contact PI or designee, if therapeutic sensation is not present. Any discomfort associated with TENS should be immediately reported to the PI or designee.

10.1.2 Risks associated with appetite loss

While appetite loss is beneficial to weight loss, severe appetite suppression may place the subject at risk for hypoglycemia and dehydration which may entail risks to alertness and other conditions. Prolonged appetite suppression can cause alterations in mood and mental acuity and impact activities of daily living (ADL).

Adverse Events: The adverse events listed below are anticipated to occur at low frequency, and the subject needs to be aware that they may occur.

<u>From TENS:</u>
Paresthesia
Burning sensation
Pain
Skin irritation (urticaria) at or near the electrode application site
Redness at site of stimulation
Mild swelling at site of electrode stimulation
Nausea
GI discomfort
Dyspepsia
Heartburn
Cramping
Gastroparesis

<u>From appetite loss:</u>
Mild hypoglycemia
Dehydration

Alterations in mood
Mild trouble sleeping
Alterations in mental acuity
Anorexia

From potential use of anti-nausea medication (PI Discretion):
Drowsiness
Dizziness
Constipation
Stomach upset
Blurred vision
Dry mouth/nose/throat may occur
Mental/mood changes (such as restlessness, confusion)
Difficulty urinating
Fast/irregular heartbeat

From potential use of Cetaphil Moisturizing Lotion
Irritation
Swelling

10.2 MINIMIZATION OF RISKS

Although all of the risks associated with the application and use of the TENS System and their respective frequencies may not be fully known at this time, the preceding risks have been identified through an extensive literature search and represent the most up to date understanding of risks associated with such a study and have been subjected to verification and validation testing to ensure that risks have been mitigated to the extent possible. All efforts will be made throughout the course of the trial to minimize these risks by:

1. Selecting an Investigator who is experienced and skilled in weight loss and TENS use;
2. Using clearly defined Inclusion/Exclusion criteria to ensure that only appropriate subjects are enrolled;
3. Ensuring that the treatment and follow-up procedures are consistent with current medical practices. Each subject will receive more extensive clinical follow-up than would typically be the case for standard care. These additional clinical follow-ups should increase the likelihood of early detection of any adverse events;
4. Utilizing a TENS designed so that it can be easily be applied and removed if necessary.

11. ADVERSE EVENTS: DEFINITIONS & REQUIREMENTS

At each evaluation, the Investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this Protocol, an AE is any undesirable clinical occurrence in a subject whether or not related to the investigational treatment. Any pre-existing condition that exhibits a change in nature, severity or degree of incidence during the clinical study is an AE. This definition does not depend on a causal relationship with the device or the Protocol requirements. AEs will be tracked and categorized as outlined within the present protocol.

Subjects are encouraged to report AEs with or without questioning (e.g., How has your health been since the last visit?). If it is determined that an AE has occurred, the Investigator will obtain all the information required to complete the AE Case Report Form.

In addition, subjects will be instructed to contact the Investigator and/or designee if any significant AEs occur between study evaluation visits. Serious AEs and unanticipated adverse device effects will be collected throughout the entire course of the study.

The Investigator will use the following definitions to assess the relationship of the AE to the use of the TENS system and/or daily electronic diary:

Not Related	▪ Not associated with device application ▪ Due to an underlying or concurrent illness or effect of another device or drug
Unlikely	▪ Little or no temporal relationship to the study device **and/or** ▪ A more likely alternative etiology exists
Possible	▪ Temporal sequence between device application and event is such that the relationship is not unlikely **or** ▪ Subject's condition or concomitant therapy could have caused the AE
Probable	▪ Temporal sequence is relevant **or** ▪ Event abates upon device application completion/removal **or** ▪ Event cannot be reasonably explained by the subject's condition
Highly Probably	▪ Temporal sequence is relevant **and** ▪ Event abates upon device application completion/removal **or** event recurs on repeated device application

11.1 SERIOUS ADVERSE EVENTS

All Serious Adverse Events (SAEs) must be reported to the PI (or designee) and sponsor within 24 hours after any clinical staff member becomes aware of the incident.

An Adverse Event is considered **serious** if the event:

- Led to a death
- Led to a serious deterioration in the health of the subject that:
  - Resulted in a life-threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in-subject hospitalization or prolongation of existing hospitalization;
  - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function;

All SAEs need to be followed until the event is resolved (with or without sequelae). The PI or designee will decide if more follow-up information is needed in case the event is not resolved at study completion. In case of death, all possible information that is available (e.g., autopsy or other post-mortem findings), including the possible relationship to the TENS System and/or daily electronic diary should be provided.

11.2 UNANTICIPATED ADVERSE DEVICE EFFECTS

An unanticipated adverse device effect is defined as any 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 the Protocol or Supplementary Protocol.

The Investigator must also report the unanticipated adverse device effect to the Institutional Review Board (IRB) within their pre-specified timeline.

12. SPONSOR RESPONSIBILITIES, RECORDS, AND REPORTS

12.1 GENERAL RESPONSIBILITIES

The Principal Investigator (PI) maintains the overall responsibility for this study including ensuring that the study is conducted according to the regulatory requirements of the United States Food and Drug Administration (FDA) (Code of Federal Regulations Title 21), Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements, the Protocol, and any conditions of approval imposed by the Institutional Review Board (IRB) and the relevant Competent Authorities. The PI will adhere to general duties as outlined by 21 CFR and GCP.

12.2 SELECTION OF CLINICAL INVESTIGATORS SITE

The PI and the site are qualified according to these criteria:

- Adequate subject population available to meet the requirements of the study
- Adequate time to be personally involved in the study
- Adequate research staff and resources to support the study
- Willingness to take the primary responsibility for the accuracy, legibility, and security of all study data
- Willingness to observe confidentiality at all times
- Associated with an IRB which satisfies all regulatory authority requirements and conducts meetings on a regular basis
- Access to appropriate emergency medical facilities if needed
- Other requirements as previously noted in Protocol

12.3 TRAINING OF INVESTIGATOR AND SITE PERSONNEL

The training of the Investigator and appropriate clinical site personnel will be the responsibility of the PI, or designee, and may be conducted during a site initiation visit or other appropriate meetings.

12.4 MONITORING

A Monitor will be assigned to perform source document review to be performed against entries on the Case Report Form for 100% of the data related to safety and performance outcomes, and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations.

All data entered by the subject onto the electronic diary will be uploaded onto a secure, central database. The data in the database are considered source documentation and are protected by auditable change logs. The data and change logs may be monitored by the Clinical Data Monitor to confirm data integrity. Further efforts to ensure data privacy and integrity include the removal of the network interface (a.k.a. SIM) card from the handheld Smart Phones used in the study to ensure that only controlled data download/upload conducted by study coordinators can occur.

At the completion of the study, the assigned monitor will perform a close-out visit to ensure that all clinical trial materials and subject data are properly documented.

If a member of the research team becomes aware that any individual associated with the study is not complying with the signed Investigator Agreement, the Protocol, the Declaration of Helsinki, or other applicable regulatory requirements, or any conditions of approval imposed by the IRB or Regulatory Authorities, the PI will either secure compliance or, failing to secure compliance, will discontinue the individual's participation in the investigation.

12.5 REPORTS

The sponsor will submit appropriate reports to the Regulatory Authorities or the investigational site as identified by local regulations. These include unanticipated adverse device effects, withdrawal of IRB approval or Regulatory Authority approval, annual progress reports, recall information, final reports and device use without Informed Consent.

12.6 RECORD MAINTENANCE

The clinical site will maintain study records for at least seven (7) years after the study is terminated or according to site and country specific requirements.

12.7 REGULATORY AUDITS

The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives during the audit process.

12.8 CONFIDENTIALITY

All data and information collected during this study will be considered confidential. All data used in the analysis and summary of this study will be anonymous, and without reference to specific study subject names. Access to study subject files will be limited to authorized personnel or designees of Investigator, and research staff. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. National regulations regarding confidentiality will be followed as appropriate.

13. INVESTIGATOR RESPONSIBILITIES, RECORDS, AND REPORTS

13.1 GENERAL RESPONSIBILITIES

Principal Investigator at the site must:

- Assure compliance of all staff to the protocol
- Ensure all staff are trained to the protocol, TENS system and electronic diary
- Obtain and maintain a copy of the Institutional Review Board (IRB) approved Informed Consent form;
- Documentation of IRB approval of the final protocol (and amendments if applicable) providing evidence of the following:
    - A statement of IRB approval for the proposed study at the institution
    - Clear identification of the reviewed documents (may be done by attaching review packet to approval letter)
    - The date the study was approved
    - A statement that the Informed Consent document (revision date referenced) has been approved (may be a separate documented letter)
    - A listing of any conditions attached to the approval
    - Identification of the approved Principal Investigator at the site
    - The signature of the IRB chairperson

Until the study is completed, the Investigator will advise the IRB of the study progress at least annually. Written approval from the IRB must be obtained yearly to continue the study. Any amendments to the protocol, as well as associated consent form changes, will be submitted to the IRB and written approval obtained prior to implementation. Serious adverse event reports will be submitted as requested by the IRB.

13.2 INFORMED CONSENT

A copy of the Informed Consent must be forwarded to the IRB. All study subjects must provide written informed consent using an IRB-approved Informed Consent. The study must be explained to the study subjects in English. The Principal Investigator at the site, or designated representative, must be available to answer all of the study subject's study-related questions. Study subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

13.3 PROTOCOL DEVIATIONS

A Protocol Deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the Protocol.

Investigators must approve any major deviations from the Protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control; however, the event is still considered a deviation and must be reported on the appropriate Case Report Form (CRF).

Deviations must be reported to the PI regardless of whether medically justifiable, pre-approved or performed to protect the subject in an emergency. Subject-specific deviations will be reported on a Protocol Deviation CRF.

Regulations require that the PI and site maintain accurate, complete and current records, including documents showing the dates of and reasons for each Protocol Deviation. For reporting purposes, Protocol Deviations are defined as major and minor as follows:

Major Deviation:	Any deviation from subject Inclusion and Exclusion criteria, subject Informed Consent procedures or authorized device use.
Minor Deviation:	Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

Minor Deviations that continue to occur may be classified as Major Deviations if corrective action is not taken to secure future compliance to the Protocol.

13.4 REPORTING REQUIREMENTS

As required by the IRB, the Investigator is responsible for reporting study progress to the IRB at least annually. The Investigator/Sponsor, as required by the local regulations, should notify the IRB in writing after completion, termination, or discontinuation of the study at the site. If the study is discontinued due to safety concerns, the Investigator will notify the IRB immediately. Timelines for notification are dependent on IRB requirements.

13.5 SOURCE DOCUMENTS

Source documents are defined as original documents, data and records. These may include hospital records, clinic and office charts, laboratory data/information, and recorded data from automated instruments, subject-reported data collected from the diary and transmitted to the secure database, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

The Investigator shall maintain all source documents as required by the Protocol, including laboratory results (e.g., pregnancy tests), subject report forms, supporting medical records, and Informed Consent forms for at least seven (7) years after the study is terminated or according to site and country specific requirements.

13.6 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/institution will permit direct access to source data/documents in order for IRB review and regulatory inspections to be performed. These data may be shared with regulatory agencies.

13.7 DATA COLLECTION

Required data for this study will be captured on standardized CRFs. CRFs will be completed and stored for data analysis. Any deficiencies identified on the CRF will be communicated to the PI by the Clinical data Monitor as appropriate.

13.8 ON-SITE AUDITS

The Investigator and/or designee must be available to respond to reasonable requests and audit queries made by authorized regulatory representatives during the audit process.

14. SITE MONITORING PROCEDURES

A Clinical Data Monitor will be responsible for the monitoring of this study. Responsibilities may be shared with Investigator or designee and include:

1. Conducting site initiation visits (training to product and protocol) after Institutional Review Board (IRB) approval and before first subject enrollment.
2. Maintaining regular contact with the site through telephone contact, email and on-site visits.
3. Assuring that the Protocol is followed; verifying that complete, timely and accurate data are submitted.
4. Monitoring subject data, including: reviewing Case Report Forms (CRFs) for completeness, verifying data to source documentation including operator worksheets retained with CRF documentation and hospital charts, and addressing problems with inconsistent, illegible and/or incomplete data.
5. Assuring that the Investigator's study file is maintained and that the site facilities continue to be adequate.
6. Conducting a close-out visit after completion of all CRFs.

During the study, the study site will be visited periodically by the Clinical Data Monitor. The Clinical Data Monitor will ensure Protocol compliance, accurate recording of results, reporting of adverse events, and record keeping. The Clinical Data Monitor will evaluate and summarize the results of each site visit in written reports, identifying any repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

15. DATA QUALITY ASSURANCE

Standard Case Report Forms (CRFs) will be provided for use at all investigational sites. The Investigator is responsible for completion and timely submission of the forms for monitoring data processing. For subject reported outcome information recorded by the subject using the diary, an audit trail will ensure any changes made to the data are properly attributed and have been reviewed and approved by the Investigator.

A Database containing data obtained from the CRFs and diary data from the handheld diary will be maintained by the PI, The management of these data will be compliant with the relevant parts of United States (US) CRF data regulations, including CFR Part 11.

Data processing will be performed by the Clinical Data Monitor.

Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that Protocol requirements are followed, and that complications, Adverse Events (AEs) and adverse device effects (ADE) are correctly reported.

Incoming data are reviewed to identify inconsistent or missing data and AEs/ADEs. Any data issues will be addressed with the Principal Investigator at the site. All hard copy forms and data files will be secured to ensure confidentiality.

16. ETHICAL REQUIREMENTS

16.1 DECLARATION OF HELSINKI

The study will be performed in accordance with ISO/EN 14155, parts 1 and 2, recommendations guiding physicians in biomedical research involving humans adopted by the 18th World Medical Assembly, Helsinki, Finland (1964 and later revisions), United States Food and Drug Administration (FDA) regulations, and International Congress on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

It is the responsibility of the Principal Investigator at the site to obtain approval of the study protocol from the competent Institutional Review Board (IRB) and to keep them informed of any Serious Adverse Events (SAEs), serious adverse device effects, and Protocol amendments. All correspondence with the IRB should be filed by the Investigator

16.2 SUBJECT INFORMATION AND CONSENT

It is the responsibility of the Investigator to give each subject full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved, and to obtain signed Informed Consent from all subjects prior to inclusion in the study unless the subject's health condition does not allow Informed Consent, in which case the national procedures will be applied.

The original, signed Informed Consent is filed with the subject study records, and a copy is provided to the subject.

16.3 SUBJECT DATA PROTECTION

The subjects will be identified in the Case Report Forms (CRFs) with a unique subject number and initials.

Per applicable regulations, the subject must be informed that the data will be stored and analyzed by computer, that national regulations for handling of computerized data will be followed, and that only the Investigator and designated research staff will have access to individual subject data. Furthermore, the subjects should be informed about the possibility of inspection of relevant parts of the hospital records by Health Authorities.

16.4 REPORTING AND COMMUNICATION OF RESULTS

All information and data generated in association with this study will be held in strict confidence and remains the sole property of PI.

16.5 CLINICAL TRIAL TERMINATION

A subject's participation in the clinical trial will be terminated if the Investigator believes it is in the subject's best medical interest or if the subject no longer complies with the clinical trial requirements. The subject may also decide to withdraw from the clinical trial at any time and terminate participation. The IRB and/or other Regulatory Authorities may decide to interrupt this clinical trial if either believes that this is necessary.

16.6 PROTOCOL MODIFICATIONS AND DEVIATIONS

The PI will submit Protocol modifications to the IRB as necessary.

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18. APPENDICES

18.1 APPENDIX 1: BMI RANGES TARGETED FOR MEN AND WOMEN ENROLLED IN STUDY [15,16]

Males (target BMI indicated by Black Bars):

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm	Underweight					Healthy						Overweight				Obese				Extremely obese				
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	37	38	39
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	32
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

Females (target BMI indicated by Black Bars):

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
HEIGHT in/cm	Underweight					Healthy						Overweight				Obese				Extremely obese				
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	37	38	39
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	23	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	32
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	14	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	29
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

18.2 APPENDIX 2: TENS UNIT USER MANUALS (ADDITIONAL FILE SUBMITTED SEPARATELY)

ELIRA

EDP ON-BODY DEVICE

PATIENT INSTRUCTIONS FOR USE

CAUTION - Investigational device. *Limited by Federal (or United States) law to investigational use.*

A: INITIAL SETUP with CLINICIAN

1 Snap on Electrode Patch

Snap the electrode patch to the EDP.

DO NOT remove the protective liner from the electrode patch.

2 Register Account

Start the Elira app on the phone provided. Proceed with registration steps.

3 Turn on EDP

Turn the EDP on by pressing and holding the button 10 seconds and releasing it.

4 Turn on EDP

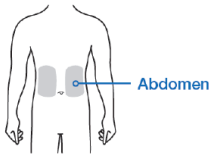
Follow the on-boarding process required by the app.

5 Remove Liner

Remove the electrode patch protective liner.

6 Place EDP

Place the EDP at T6 dermatome location.



WARNINGS

SYSTEM COMPONENTS

ELIRA

Elira Therapuetics
anNdsakfal
kNADkoasdf, ha 23443

C: DAILY USE

1 Snap on the Patch

Upon waking remove EDP from charging pad.

DO NOT remove the protective liner from the electrode patch.

2 Turn on EDP

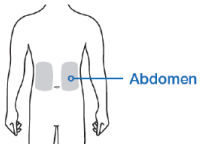
Turn the EDP on by pressing and holding the button 10 seconds and releasing it.

3 Remove Liner

Remove the electrode patch protective liner.

4 Place EDP

Place the EDP at T6 dermatome location.



5 Treatment cycle

Follow prescribed treatment cycle.

6 Remove EDP

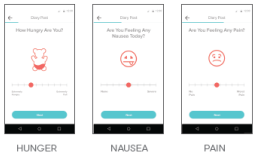
Remove EDP before bed, apply the protective liner to the electrode patch for overnight storage

7 Charge EDP Overnight

Place EDP on charger. Disconnect Bluetooth connection

8 Log Dairy Post

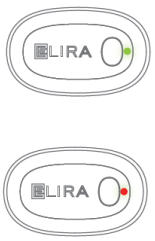
Complete diary entry for the day.



D: PATCH LIFE

The electrode patch life will vary, depending on care and skin type, but should be replaced when it no longer adheres well to the skin. If your skin type is oily or has residue on it, you may need to replace the electrode pad more frequently.

E: SYSTEM STATUS



THERAPY LIGHT

The Status LED blinks **GREEN** once ever 10 seconds while the device is in Therapy mode.

ERROR LIGHT

Low Battery - The Status LED blinks **RED** in high frequency.

Error Events:
Impedance out of range
Temperature out of range
Max Session Count Reached
Device Mode Error
The Status LED blinks **RED** in low frequency.

CAUTION - **Investigational device.** *Limited by Federal (or United States) law to investigational use.*

ELIRA

18.3 APPENDIX 3: PHQ-9 QUESTIONNAIRE

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING *0* + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Subject Initials:_____

Date:_____

18.4 APPENDIX 4: TFEQ-R18V2 [17]

The Three-Factor Eating Questionnaire

Please read each statement and select from the multiple-choice options the answer that indicates the frequency with which you find yourself feeling or experiencing what is being described in the statements below.

1. When I smell a delicious food, I find it very difficult to keep from eating, even if I have just finished a meal.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

2. I deliberately take small helpings as a means of controlling my weight.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

3. When I feel anxious, I find myself eating.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

4. Sometimes when I start eating, I just can't seem to stop.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

5. Being with someone who is eating often makes me hungry enough to eat also.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

6. When I feel blue, I often overeat.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

7. When I see a real delicacy, I often get so hungry that I have to eat right away.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

8. I get so hungry that my stomach often seems like a bottomless pit.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

9. I am always hungry so it is hard for me to stop eating before I finish the food on my plate.

   Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

10. When I feel lonely, I console myself by eating.

    Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

11. I consciously hold back at meals in order not to weight gain.

    Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

12. I do not eat some foods because they make me fat.

Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

13. I am always hungry enough to eat at any time.

Definitely true (4) / mostly true (3) / mostly false (2) / definitely false (1)

14. How often do you feel hungry?

Only at meal times (1) / sometimes between meals (2) / often between meals (3) / almost always (4)

15. How frequently do you avoid "stocking up" on tempting foods?

Almost never (1) / seldom (2) / moderately likely (3) / almost always (4)

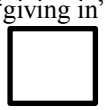
16. How likely are you to consciously eat less than you want?

Unlikely (1) / slightly likely (2) / moderately likely (3) / very likely (4)

17. Do you go on eating binges though you are not hungry?

Never (1) / rarely (2) / sometimes (3) / at least once a week (4)

18. On a scale of 1to 8, where 1 means no restraint in eating (eating whatever you want, whenever you want it) and 8 means total restraint (constantly limiting food intake and never "giving in"), what number would you give yourself?



Revised 18-Item (Karlsson et. Al. 2000)

18.5 APPENDIX 5: VAS AND DAILY DIARY APPLICATION

Recommended primary scales for self-reported appetite in healthy adults[a]

Scale	Question	Anchors	
		Low	High
Hunger	How hungry are you?	Not at all	Extremely As hungry as I have ever felt
Fullness	How full are you?	Not at all	Extremely As full as I have ever felt
Satiety	How satiated are you?	Not all	Extremely
Desire	How strong is your desire to eat?	Very weak Extremely low	Very strong Extremely high
Prospective consumption (Quantity)	How much do you think you could (or would want to) eat right now?	Nothing at all	A very large amount

[a]Line scales 100-150 mm (paper) or appropriate length for electronic capture systems are to be used for each of these questions.

ELIRA THERAPEUTICS

Appetite Assessment Diary
Protocol: CD-004

Subject Initials: _____ Subject Number: ___ ___ - ___ ___ ___

Directions: Answer each question abut how you are feeling by drawing a mark (|) through the horizontal line of each question.

Please complete prior to mealtime. TIME:_____ □AM □PM DATE:_____

Table 1 Please indicate below your level of nausea:

None — Worst Ever

Please indicate below your level of fullness:

None — Worst Ever

Please indicate below your level of bloating:

None — Worst Ever

Please indicate below your level of abdominal pain:

None — Worst Ever

To be completed by study staff:

Scoring:

Table One: 1-_____ 2-_____ 3-_____ 4-_____

Table Two: 1-_____ 2-_____ 3-_____ 4-_____

Table Three: 1-_____ 2-_____ 3-_____ 4-_____

Table 2 How Satisfied do you feel?

I am not hungry at all — I have never been more hungry

How full do you feel?

I am completely empty — I cannot eat another bite

How hungry do you feel?

Not full at all — Totally full

How much do you think you can eat?

Nothing at all — A lot

Table 3 Would you like to eat something sweet?

Yes, very much — No, not at all

Would you like to eat something salty?

Yes, very much — No, not at all

Would you like to eat something savory?

Yes, very much — No, not at all

Would you like to eat something fatty?

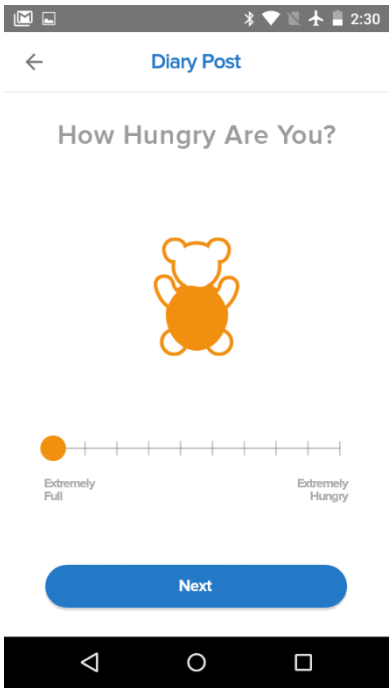
Yes, very much — No, not at all

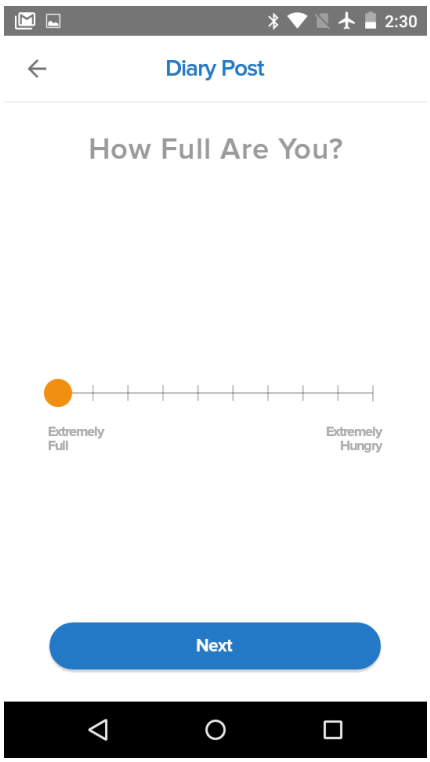
18.6 APPENDIX 6: SCHEDULE OF EVENTS

STUDY PERIOD	SCREENING/ BASELINE	ENROLLMENT/ RANDOMIZATION	THERAPY			END OF STUDY[7]
VISIT #	VISIT 0	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5
WEEK #	-1 WEEK	WEEK 0	WEEK 1	WEEK 4	WEEK 8	WEEK 12
VISIT WINDOW[1]	±7 DAYS	±7 DAYS	±7 DAYS	±7 DAYS	±7 DAYS	±7 DAYS
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical History	X					
Diet History	X					
Physical Exam	X					X
T6/T7 dermatome assessment	X[3]	X[3]	X[4]	X[4]	X[4]	X[4]
Blood Pressure	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Height	X					
Weight	X	X	X	X	X	X
Laboratory Requisition - Blood Tests [2]	X					X
Urine Pregnancy Test (WOCBP)	X	X[6]				X
Administration of Patient Preference Survey	X					X
Administration of PHQ-9	X					X
Administration of TFEQ-R18V2		X	X	X	X	X
Provide/Train on Paper Diaries[3]	X	X	X	X	X	
Collect and Review Paper Diaries[3]		X	X	X	X	X
Randomization[5]		X				
Encourage 1200 calorie diet		X	X	X	X	
Provide Electronic Scale		X				
Provide and Train on Electronic Diary[4]		X	X	X	X	
Collect and Review Electronic Diary[4]			X	X	X	X
Provide and Train on TENS Unit and Patches[4]		X	X	X	X	
Collect and Examine TENS Unit and Patches[4]			X	X	X	X
Provide/Instruct on TENS Clean-Cote Skin Wipes and/or Alcohol Prep Pads[4]		X	X	X	X	
Provide/Instruct on Cetaphil Lotion[4]		X	X	X	X	
Assessment of Adverse Events	X	X	X	X	X	X
Assessment of Adverse Device Effects[4]		X	X	X	X	X
Schedule next visit	X	X	X	X	X	
Study Exit						X

1 – All visits are ± 7 days
2 – Blood tests include HbA1c, lipid panel, CMP
3 – To be completed for control and treatment group
4 – To be completed for treatment group only
5 – Randomization into control or treatment group
6 – Complete UPT only if not completed at screening
7 – Complete all procedures at End of Study or Early Termination Visit

18.7 APPENDIX 7: ELECTRONIC DIARY APPLICATION (SEE SAMPLES SCREEN SHOTS)




2:30
Diary Post
How Full Are You?
Extremely Full
Extremely Hungry
Next

18.8 APPENDIX 8: LIST OF POTENTIAL DRUG INTERACTIONS

	Weight *positive* medications (cause weight gain)	Weight *negative* medications (cause no gain* or weight loss)
DIABETES	Glipizide Glyburide Insulin Pioglitazone Rosiglitazone	Acarbose* Exanatide Glimepiride* Liraglutide Metformin Sitagliptan*
HYPERTENSION	Atenolol Clonidine Hydralazine Labetalol Prazosin Terazosin Valsartan	Amlodipine Captopril* Carvedilol* Enalapril* Furosemide Hydrochlorathiazide* Lisinopril Losartan* Metoprolol* Olmesartan
PSYCHIATRIC	Citalopram Clozapine Lithium MAO-I Mirtazapine Olanzapine Paroxetine Phenothiazines Risperdone TCA	Amphetamines Buproprion Escitalopram* Fluoxetine Sertraline
CHRONIC PAIN	Amitriptyline Celecoxib Gabapentin Methadone Pregabalin	Acetaminophen* Baclofen* Carisoprodol* Cyclobenzaprine* Diclofenac* Fentanyl Hydromorphone Ibuprofen* Morphine Naproxen* Tramadol

FIGURE 1: Commonly prescribed weight positive, negative, and neutral* medications.

*List of drugs includes some pharmaceuticals that may impact study participation. May not be complete and is up to PI discretion.

18.9 APPENDIX 9: PATIENT PREFERENCE SURVEY

Elira Concept Test

8-10-17

1. Which of the following topics are you interested in?
    a. Investing
    b. Weight loss
    c. Sports
    d. Working out in the gym
    e. Yoga
    f. Martial Arts
    g. Camping
    h. Hunting / Fishing
    i. Hiking / Bicycling
    j. Cars / Motorcycles
    k. Traveling
    l. Fine dining
    m. Home improvement
    n. Fitness / Nutrition / Health
    o. Movies / Entertainment
    p. Politics / current events / news
    q. Books
    r. Shopping
    s. None of the above

2. Are you interested in losing weight?
    a. Yes
    b. No

3. Please select your gender.
    a. Male
    b. Female
    c. Prefer not to respond

4. Please select your age.
    a. Under 18
    b. 18 – 24
    c. 25 – 34
    d. 35 – 44
    e. 45 – 54
    f. 55 – 64
    g. 65 – 74
    h. 75 or older

5. How much weight do you think you need to lose?
    a. None
    b. Less than 5 lbs
    c. 5 – 10 lbs
    d. 11 – 15 lbs
    e. 16 – 20 lbs
    f. More than 20 lbs

g. Not sure

6. Please enter your height in feet and inches.

7. Please enter your weight in lbs.

8. A number of weight loss programs offer the potential to lose 1-2 lbs per week. Do you consider this a reasonable amount of weight for you to lose per week in a weight loss program?
   a. Yes
   b. No, I would expect to lose less per week
   c. No, I would expect to lose more per week

9. Which, if any, of the following have you attempted in order to lose weight in the past? Select all that apply.
   a. Dieting on your own (not through a specific program)
   b. Dieting with online coaching or support (like MyFitnessPal)
   c. Exercise or increasing amount of exercise
   d. Commercial weight loss program (Jenny Craig / Weight Watchers, etc.)
   e. Gym membership
   f. Medical weight loss through a physician
   g. Behavioral modification therapy
   h. Prescription diet pills or other prescription medications
   i. Surgical or other invasive procedures
   j. Body sculpting targeting specific areas, like Cool Sculpting or liposuction
   k. Other (please specify)
   l. I haven't tried to lose weight in the past

10. Please rate your level of success, if any, with past weight loss attempts.

	Very successful	Moderately successful	Slightly successful	Not at all successful	I didn't give it a chance
Dieting on your own (not through a specific program)	a.	b.	c.	d.	e.
Dieting with online coaching or support (like MyFitnessPal)	a.	b.	c.	d.	e.
Exercise or increasing amount of exercise	f.	g.	h.	i.	j.
Commercial weight loss program (Jenny Craig / Weight Watchers, etc.)	a.	b.	c.	d.	e.
Gym membership	a.	b.	c.	d.	e.
Medical weight loss through a physician	a.	b.	c.	d.	e.
Behavioral modification therapy	a.	b.	c.	d.	e.
Prescription diet pills or other prescription medications	a.	b.	c.	d.	e.
Surgical or other invasive procedures	a.	b.	c.	d.	e.

Body sculpting targeting specific areas, like Cool Sculpting or liposuction	a.	b.	c.	d.	e.
Other	a.	b.	c.	d.	e.

11. Which of the following medical aesthetics or cosmetic procedures, if any, would you consider? Select all that apply.
    a. Plastic surgery (e.g., face lift, tummy tuck, etc.)
    b. Laser dermal treatments
    c. Injectibles like Botox
    d. Dermal fillers like Restylane and Juvederm
    e. Targeted body sculpting or fat elimination like liposuction or Cool Sculpting
    f. Would not consider any of the above

12. What is the primary reason you want to lose weight?
    a. Health-related reasons
    b. Lifestyle reasons (want to be able to be more active, etc.)
    c. Recommended by my Company's wellness program
    d. Special event (wedding, reunion, party, etc.)
    e. Just want to look better
    f. Other (please specify)

13. What other reason(s), if any, do you have for wanting to lose weight? Select all that apply.
    a. Health-related reasons
    b. Lifestyle reasons (want to be able to be more active, etc.)
    c. Recommended by my Company's wellness program
    d. Special event (wedding, reunion, party, etc.)
    e. Just want to look better
    f. Other (please specify)
    g. No other reason

14. Is it easy or difficult for you to lose weight?
    a. Very easy
    b. Somewhat easy
    c. Sometimes easy, sometimes difficult
    d. Somewhat difficult
    e. Very difficult
    f. I've never tried to lose weight before

15. What are your primary barriers to weight loss? Select all that apply.
    a. Time
    b. Cost
    c. Willpower
    d. Appetite control
    e. Fear of failure
    f. Concerns about side effects of medication or surgery
    g. Other (please specify)

16. Please rank your weight loss goals in order of importance. "1" should be the most important.
    a. Achieve a healthy metabolism
    b. Control my appetite
    c. Lose weight
    d. Achieve a healthy diet

e. Increase fitness
f. Normalize my body mass index (Achieve a BMI of less than 25)
g. Improve my body shape
h. Become leaner
i. Improve my looks

Please evaluate the following concept closely and answer the questions that follow.

An Introduction to Elira

Concept Statement

Elira represents an entirely new way to lose weight by controlling appetite. Simply put, eating too much typically results in excess weight, and the right way to improve health is to lose that weight. The Elira electronic skin patch helps make weight loss easier by providing a means to suppress appetite by causing a feeling of fullness (or satiety). This in turn allows you to "reset" your caloric intake and better control hunger pangs and the urge to snack excessively. Think of Elira as a personal dietary assistant that is typically worn during daylight hours for a 12-week course of treatment.

Elira is intended to be a FDA-approved, wearable, electronic skin patch that is easy to use and non-invasive (see picture above). It is controlled by a smartphone and delivers electrical stimulation to specific sensory nerves in your abdomen which results in a feeling of fullness, making it easier to maintain a weight loss diet. The Elira device is intended to be worn during waking hours and it is programmed to deliver stimulation sessions (typically 3 per day) around mealtimes. The user does not have to do anything to activate the therapy – it is all done automatically.

Elira treatments are not painful – when activated, users feel a tingling sensation to the skin. No significant side effects have been observed. What makes Elira unique are its medical and scientific credentials based on clinical trials, coupled with the ease of use of a smartphone-controlled, unobtrusive skin patch.

Other FDA approved medical devices for weight loss typically require surgical implantation with all of the risks and side effects associated with an invasive procedure. Also, implanted devices tend to be very expensive with costs ranging in the thousands of dollars – costs that are often not covered by insurance. Elira is intended to be an entirely non-invasive, FDA-approved medical device for weight loss and appetite control without any of the risks and costs associated with surgical implantation. It is designed to be affordable and extremely safe, allowing users a chance to avoid the downsides of either surgery or drugs, and is expected to result in greater weight loss than diet & exercise alone.

17. Which best describes how you feel about buying Elira, assuming it fits your budget?
    a. Definitely would buy
    b. Probably would buy
    c. Might or might not buy
    d. Probably would not buy
    e. Definitely would not buy

18. Which best describes how much you think you would like or dislike the Elira device?
    a. Very appealing
    b. Somewhat appealing
    c. Neither appealing nor unappealing
    d. Somewhat unappealing
    e. Very unappealing

19. What, if anything, do you like MOST about this product?

20. What, if anything, concerns you or do you dislike about this product?

21. How believable do you find this Elira device to be after reading the statement above and assuming that Elira is approved by the FDA as a medical device for weight loss?
    a. Very believable
    b. Somewhat believable
    c. Neither believable nor unbelievable
    d. Somewhat unbelievable
    e. Very unbelievable

22. How willing would you be to wear the Elira device daily for 3 months if it resulted in your achieving your weight loss objectives?
    a. Very willing
    b. Moderately willing
    c. Slightly willing
    d. Not at all willing

23. Which of the following physicians would you be most likely to visit in order to obtain the Elira device?
    a. General/Family Practitioner
    b. OB/GYN
    c. Cosmetic Surgeon
    d. Medical Weight Loss Clinic or Spa
    e. Cosmetic Dermatologist
    f. Therapist
    g. Other (please specify)

24. How would you rate this product in terms of being new and different from other weight loss products that you are familiar with?
    a. Very unique
    b. Somewhat unique
    c. Not at all unique

25. How would you improve the device?

26. The following are three medical weight loss treatments that have been shown to be effective, but which have certain patient eligibility requirements:
    a. Bariatric surgery - permanently reducing the size of the stomach or placing a band around it
    b. Endogastric implants - a procedure using an endoscope to place a balloon in the stomach
    c. Prescription weight loss drugs

    For each of these treatments, how likely would you be to talk to your health care provider about your eligibility for the treatment, and about the costs and side effects associated with it?

	Highly likely	Somewhat likely	Not sure	Somewhat unlikely	Not at all likely	Already looked into it
Bariatric surgery	a.	b.	c.	d.	e.	f.
Endogastric implants	a.	b.	c.	d.	e.	f.
Prescription weight loss drugs	a.	b.	c.	d.	e.	f.

27. Diet and exercise have been shown to be effective ways to lose weight or control one's weight. However, success depends on one's ability to adhere to a dietary or exercise plan. If Elira is able to make it <u>easier</u> for you to control your appetite and lose more weight than through diet and exercise alone, would you consider purchasing an Elira device, assuming it fits your budget?
    a. Highly likely
    b. Somewhat likely
    c. Not sure
    d. Somewhat unlikely
    e. Not at all likely

    If your answer is No, then what would make Elira attractive enough for you to purchase it? (Open Ended)

28. Assuming Elira fits your budget, if using Elira helped you lose <u>15% more weight</u> than you would have lost by diet and exercise alone, how likely would you be to want to try it?
    a. Highly likely
    b. Somewhat likely
    c. Not sure
    d. Somewhat unlikely
    e. Not at all likely

28. How likely would you be to consider using an Elira device if it was shown to be safe and effective in helping you achieve your weight loss goals, but was not covered by insurance provided it cost no more than **$25/month** over a 12-month period?
    a. Highly likely
    b. Somewhat likely
    c. Not sure
    d. Somewhat unlikely
    e. Not at all likely

29. How likely would you be to consider using an Elira device if it was shown to be safe and effective in helping you achieve your weight loss goals, but was not covered by insurance provided it cost no more than **$50/month** over a 12-month period?
    a. Highly likely
    b. Somewhat likely
    c. Not sure
    d. Somewhat unlikely
    e. Not at all likely

30. How likely would you be to consider using an Elira device if it was shown to be safe and effective in helping you achieve your weight loss goals, but was not covered by insurance provided it cost no more than **$100/month** over a 12-month period?
    a. Highly likely
    b. Somewhat likely
    c. Not sure
    d. Somewhat unlikely
    e. Not at all likely

31. Following is a list of features that we hope to incorporate into our Elira device in the future. Please evaluate each and rank based on importance. “1” should be the most important and “5” should be least important.
    a. Rescue sessions (i.e., the ability to schedule additional Elira treatments in-between mealtimes in order to curb the need to snack.)
    b. Ability to connect with other devices like Fitbit so as to integrate exercise information
    c. Ability to connect with social networks so that you aren't alone while dieting to lose weight
    d. Ability to connect with dietary apps like MyFitnessPal or other online weight loss programs so as to integrate online dietary advice, calorie counting programs, healthy recipes, etc.
    e. Access to live dietary coaching and support
    f. Ability to directly order healthy foods for home delivery

32. Do you consider yourself to be one of the following? Select all that apply.
    a. Vegetarian
    b. Vegan
    c. Organic Foodie
    d. Low-carb Dieter (such as Paleo)
    e. None of the above

33. What was the highest level of education you have completed?
    a. Less than high school graduate
    b. High school graduate
    c. Trade school
    d. Some college
    e. Graduated college
    f. Post graduate work
    g. Prefer not to answer

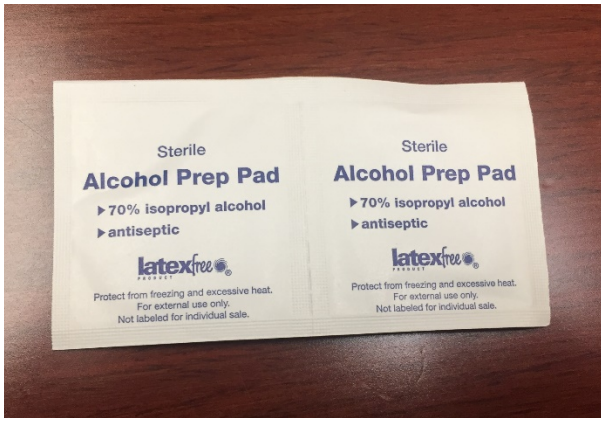
34. Which one of the following best describes your marital status?
    a. Married
    b. Single
    c. Divorced
    d. Separated
    e. Other
    f. Prefer not to answer

35. Which one of the following best describes your current employment status?
    a. Employed full time
    b. Employed part time
    c. Full-time mother
    d. Student
    e. Not employed
    f. Other
    g. Prefer not to answer

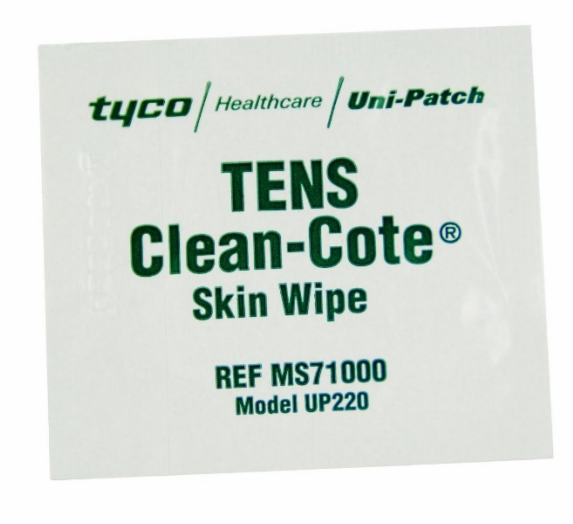
36. Which one of the following best describes your ethnic background?
    a. Caucasian (not Hispanic or Latino)
    b. Hispanic or Latino
    c. African American
    d. Asian or Pacific Islander
    e. Other
    f. Prefer not to answer

37. Which one of the following groups contains your total annual household income before taxes?
    a. Under $30,000
    b. $30,000 - $49,999
    c. $50,000 - $74,999
    d. $75,000 - $99,999
    e. $100,000 - $124,999
    f. $125,000 - $149,999
    g. $150,000 or more
    h. Prefer not to answer

18.10 APPENDIX 10: MISCELLANEOUS TRIAL COMPONENTS


Sterile
Alcohol Prep Pad
▸70% isopropyl alcohol
▸antiseptic
latexfree
Protect from freezing and excessive heat.
For external use only.
Not labeled for individual sale.
Sterile
Alcohol Prep Pad
▸70% isopropyl alcohol
▸antiseptic
latexfree
Protect from freezing and excessive heat.
For external use only.
Not labeled for individual sale.


Directions:
Apply topically as needed
to cleanse intended area.
See box for complete
Drug Facts information.
Discard after single use.
Flammable, keep away
from fire or flame.
RK12YMS
LOT 67017030014
Directions:
Apply topically as needed
to cleanse intended area.
See box for complete
Drug Facts information.
Discard after single use.
Flammable, keep away
from fire or flame.
RK12YMS
LOT 67017030014


tyco / Healthcare / Uni-Patch
TENS
Clean-Cote®
Skin Wipe
REF MS71000
Model UP220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