THE SAHARA STUDY

An Evaluation of the Safety and Effectiveness of the N-SWEAT Patch for the Treatment of Primary Axillary Hyperhidrosis or Excessive Axillary Sweating

Clinical Study PROTOCOL
(CB-CLP-001)
Version: Rev E

Date: 26 April 2021

IDE NUMBER: G200196
NCT: 04599907

CONFIDENTIAL

1. PROTOCOL SYNOPSIS

GENERAL INFORMATION	
STUDY TITLE	An Evaluation of the Safety and Effectiveness of the N-SWEAT Patch for the Treatment of Primary Axillary Hyperhidrosis or Excessive Axillary Sweating
INVESTIGATIONAL DEVICE	N-SWEAT Patch
STUDY NAME	The Sahara Study
PATCH CHARACTERISTICS	• A non-invasive energy-based patch, which, when in contact with sweat, produces thermal energy intended to target and temporarily inactivate sweat glands leading to a reduction in sweat production • Patch is self-adhesive with a layer of alkali metal foil pressed into a polyimide film • Device is inert until it comes into contact with water (sweat) • Patch is applied to the axillae for up to 3-minutes in a medical office, it is then removed and disposed of by medical staff.
CONTROL DEVICE	Sham Patch
SPONSOR/ MANUFACTURER	Candesant Biomedical, Inc
INDICATION FOR USE (proposed)	N-SWEAT Patch is indicated for treatment of excessive axillary sweating or primary axillary hyperhidrosis in individuals 22 years of age or older.
REGULATORY STATUS	The N-SWEAT Patch is under clinical investigation in the US for this proposed indication

STUDY OVERVIEW	
DESIGN	Prospective, multi-center, randomized, blinded, sham-controlled
OBJECTIVE	The pivotal study is intended to evaluate the safety and effectiveness of the N-SWEAT Patch for use in subjects with excessive axillary sweating or primary focal axillary hyperhidrosis. Safety of the N-SWEAT Patch will be confirmed by assessing the occurrence of local skin reactions, treatment-related adverse events (AEs) and Serious Adverse Events (SAEs). Primary demonstration of effectiveness will be assessed by a significant improvement (reduction) in Hyperhidrosis Disease Severity Score (HDSS) in subjects treated with the N-SWEAT Patch versus sham control subjects. Secondary and additional endpoints based on complementary clinical instruments have been included to further demonstrate performance.
POPULATION	Healthy male and female subjects in good general health who sweat excessively in the axillae or have primary focal axillary hyperhidrosis will be considered for study participation. Enrollment is limited to subjects with HDSS scores of 3 or 4.
STUDY DURATION	ROLL-IN COHORT: 1.5 months enrollment / 3.5 months follow-up RANDOMIZED COHORT: 3 months enrollment / 3.5 months follow-up

ENROLLMENT AND FOLLOW-UP	
ROLL-IN COHORT	10 N-SWEAT treated subjects at 1 Study Site
RANDOMIZED COHORT	Up to 110 Subjects at up to 14 Study Sites • Subjects will be randomized 1:1; treated with N-SWEAT or sham patch, stratified by HDSS 3 and HDSS 4 at Baseline • At least 50 subjects will be treated in each group. • Up to 10 additional subjects may be enrolled to account for loss to follow up or critical missing data
PHONE CALLS	24 hours (±12 hours) and 2-weeks (± 2 days) post-treatment
CLINIC VISITS	Required: 48-72 hours (± 24 hours) and 4-week (± 3 days) Recommended (phone call permitted): 6-, 8-, 10-, 12-weeks (± 3 days) On-site or telehealth visit should be scheduled within 24 hours of a treatment site AE with a clinic visit required for any burn injury.
ELECTRONIC	Weekly (beginning 1-week post treatment); HDSS and Quality of Life (QoL) surveys (QoL-7, Impact, Bother, etc.) via cell phone, tablet or computer
ASSESSMENTS	• Gravimetric Sweat Production (GSP) Assessments will be conducted at screening, baseline and 4-week clinic visits only. • In addition, a written daily diary will be distributed to subjects to track treatment responses and outcomes. This will be returned at the 4-week study visit.
EXTENDED FOLLOW-UP COHORT	Subjects that reach the final Sahara Study visit (12 weeks) and are still responding to treatment (i.e. HDSS has not returned to Baseline) will be invited to continue follow-up • Eligible subjects will provide consent prior to being enrolled into this cohort, within 4 weeks of completing their 12-week visit. • Subject enrolled in this cohort will not undergo any additional treatment, their participation will include extended follow-up only through 24-weeks post treatment or when HDSS returns to Baseline (whichever occurs first) • Subjects will be asked to continue weekly electronic surveys until participation is complete. • Phone Calls with the site study teams will be scheduled at 16-weeks, 20-weeks and 24-weeks post treatment during participation

STUDY ENDPOINTS	
SAFETY ASSESSMENT	Safety will be confirmed by an assessment of the occurrence of local skin reactions, treatment-related AEs and SAEs.
PRIMARY EFFICACY ENDPOINT	Primary efficacy endpoint will be assessed as the proportion of patients with HDSS of 1 or 2 at 4-week follow-up by treatment group
SECONDARY EFFICACY ENDPOINTS	The first evaluation of all secondary endpoints will occur at 4-week time point. These endpoints will be evaluated at all available time points. 1. Mean improvement in QoL scale Bother by treatment group 2. Mean improvement in QoL scale Impact by treatment group 3. Proportion of patients with improvement of at least 2 grades from baseline to 4-weeks in HDSS by treatment group 4. Proportion of subjects with at least 50% improvement in GSP from baseline 4-weeks in N-SWEAT treated group only.
OBSERVATIONAL ENDPOINTS	• Baseline-adjusted mean improvement in QoL-7 instrument assessed by treatment group • Composite - proportion of patients with HDSS 1 or 2 AND 50% improvement in GSP assessed by treatment group • Composite - proportion of patients with HDSS 1 or 2 AND 75% improvement in GSP assessed by treatment group • Duration of efficacy: time from treatment to first observed reversion to HDSS 3 or 4 (median duration of efficacy will be calculated). Also performed for first reversion to subject's baseline HDSS. • Mean change from baseline over time in GSP compared between treatment groups; Change in GSP at individual timepoints.

ELIGIBILITY: INCLUSION CRITERA

1. Signed written informed consent, including authorization to release health information. (Subject must be able to read informed consent independently since subjective feedback is required)
2. At least 22 years old at the time of consent.
3. Female or male, who experiences excessive sweating or has been diagnosed with primary axillary focal hyperhidrosis and is in otherwise good general health
4. GSP >50mg/5min in each axilla at room temperature/humidity (20-25.6°C/20-80%) at both screening and baseline
5. Reports a score of HDSS score of 3 or 4 at both screening and baseline
6. Subject agrees to avoid use of topical aluminum compounds, antiperspirants, anticholinergic medications or steroids for the duration of study participation.
7. Subject is willing and able to follow instructions and likely to complete all requirements for the study including hair removal
8. Women of child-bearing age must have a negative pregnancy test at screening and must be practicing and willing to continue an effective method of birth control from screening visit until study completion.

ELIGIBILITY: EXCLUSION CRITERIA

1. Active skin disease, irritation, or abrasions at either axilla based on physical examination by physician at Baseline.
2. Subject's medical history is indicative of secondary or diffuse hyperhidrosis and/or subject has a diagnosis of secondary or diffuse hyperhidrosis
3. GSP exceeds 300 mg/5min in either axilla at either screening or baseline
4. GSP readings differ by more than 100% in either axilla between screening and baseline
5. Hair bearing area of the axillae is more than 6 in length and/or 2.75 in width or is not able to be fully covered by the active (foil) area of one study patch
6. Treatment with botulinum toxin for excessive sweating or hyperhidrosis within 1 year
7. Undergone any procedures, including for hyperhidrosis, which may affect the axillary areas (e.g., laser hair removal within the last 3 months; Skoog procedure, any type of sympathectomy, gland excision, or other surgery; thermolysis, liposuction; or iontophoresis) or is planning to undergo any of these procedures during the course of the study
8. Use of prescription, prescription strength, or clinical strength topical aluminum compounds for axillary hyperhidrosis (e.g., Maxim, Drysol, Certain Dri) for 30 days prior to screening
9. Use of over-the-counter antiperspirants and antiperspirant deodorants for 2 days prior to screening
10. Concurrent use of oral or topical anticholinergic medications (including Qbrexza, glycopyrronium, glycopyrrolate, clonidine, atropine, Bellargal-S), beta blockers, calcium channel blockers, or other topical or systemic treatments that may affect hyperhidrosis symptoms starting at screening visit.
11. Use of a topical steroid (e.g., hydrocortisone, triamcinolone) within or around the axilla (planned treatment areas) within 14 days prior to screening
12. Presence of a psychological disorder which may interfere with perception of self or perception of severity of sweating.
13. Use of neuromodulator (e.g. Botox, Dysport, Xeomin) to the hands in the prior 12 months,
14. Patients with unevaluated lymphadenitis or enlarged lymph nodes should also not be enrolled in case the lymph nodes are reactive or potentially indicative of cancer,
15. Subjects with allergy to any of the ingredients of the patch,
16. Patients with conditions or prior treatments in the axilla that may limit the feeling of pain right away or are associated with decreased sensitivity, (e.g. diabetic patients or patients with any other neurological diseases),
17. Patients at risk for scarring, collagen vascular diseases, Hidradenitis suppurativa. Patients treated with isotretinoin may also experience severe scarring

TREATMENT APPROACH ***Note: There is no difference in the treatment approach for the test vs. control groups. In the randomized cohort personnel are blinded to treatment assignments***	
INSPECTION	Final examination of the axilla to confirm freedom from any skin disease or irritation, including both visual and tactile assessment of any irregularities. Axilla must be free of abrasions, broken skin, or other conditions of concern. If both axillae do not meet this requirement, do not proceed with treatment.
IDENTIFICATION OF TREATMENT SITE	The target treatment area should be chosen by identifying a relatively flat area with the highest concentration of hair follicles; intended to maximize contact with the location of sweat production. For convenience, site may be marked.
PREP OF TREATMENT SITE	The subject's axilla (treatment site) will be cleaned with alcohol to ensure that no residual deodorant or other residue remains in the target treatment area. The area shall then be thoroughly dried.
PATCH APPLICATION	The clinician removes the release liner and applies the patch to the prepared and dried axillary area. The patch is held in place by the adhesive backing for the duration of the treatment, which is **no longer than** 3-minutes. Throughout the treatment period the clinician will observe the subject closely. If the subject experiences discomfort or pain that is significant (8 or greater pain level on a Wong-Baker FACES pain scale) the patch should be removed **immediately** even if it has been in place for less than 3 minutes.
POST TREATMENT	Immediately following patch removal, the treatment area will be cleansed thoroughly with water. A gauze pad soaked with water should be used to wipe the area a few times. This step should be repeated until the subject does not feel any residual effects. The patch should be placed into the disposal solution per instructions provided.
SECOND AXILLA	All the sequential steps above will be repeated for treatment of the second axilla in the same treatment visit.

RANDOMIZATION	
RANDOMIZATION	Subjects in the randomized cohort will be randomized to one of two treatment groups in a 1:1 ratio to receive a single administration of N-SWEAT Patch or sham control patch in both axillae. The randomization will be stratified by HDSS 3 vs. 4 at baseline.
BLINDING	• Subjects in the randomized cohort will remain blinded to their treatment assignment • Site personnel conduction follow-up evaluations will be kept blinded • The treatment assignments will not be shared with the study sites; the sponsor will provide devices accurately labeled to allocate treatment assignments • The sponsor will identify only those who need to be unblinded to conduct the study, all others at the sponsor will remain blinded • The statistician conducting the data analysis; a different statistician responsible for the randomization codes will be unblinded to the treatment assignments.

STATISTICAL ANALYSIS	
SAFETY ANALYSIS	Adverse Events summaries will be presented overall, by severity, by device relatedness as determined by investigator (defined as related or with missing relationship). The SAE's will be summarized by treatment group. Evaluation of local skin reactions will also be tabulated. Summaries will be presented by treatment group and for all patients. Patient listings of SAEs and adverse events leading to withdrawal will be presented. Adverse device events, serious adverse device events and unanticipated adverse device events will be summarized by treatment group. The occurrence of local skin reactions, device-related AEs, and SAEs will be assessed to confirm device safety. This safety analysis will include all enrolled subjects (both Roll-in and Randomized Cohorts).
PRIMARY ENDPOINT EFFICACY ANALYSIS	Proportions of subjects in the randomized cohort with HDSS of 1 or 2 at 4-weeks post-treatment will be compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HDSS value 3 vs. 4.
SECONDARY EFFICACY ENDPOINT ANALYSIS	All secondary endpoints will be hierarchically tested at the same 0.05 two-sided level. Each secondary endpoint will be tested if and only if the previous endpoint demonstrated statistical significance at the 0.05 two-sided level. If prior endpoint on the list did not show statistical significance, testing will be stopped and data will be analyzed descriptively.

DATA SAFETY MONITORING BOARD	
Chairperson:	Patricia Walker, MD, PhD
Members:	Suzanne Kilmer, MD Lisa Donofrio, MD
Role1:	To convene as needed for review of Adverse Events related to stopping rules and to determine a root cause analysis of these events
Role 2:	To conduct a monthly blinded review of all AEs reported during enrollment and until the final subject has reported for 4-week follow-up
Role 3:	If warranted, to request unblinding and fully investigate any potential safety signal. This investigation may result in a recommendation to stop the clinical study if the findings indicate an unacceptable or unknown safety risk.

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An Evaluation of the Safety and Effectiveness of the N-SWEAT Patch for the Treatment of Excessive Axillary Sweating or Primary Axillary Hyperhidrosis

Investigator Attestation of Receipt and Understanding

I, the undersigned, certify that I have reviewed and understand the contents of this protocol and further agree to abide by the terms described herein. I am in receipt of and understand the contents of the below-listed items:

- The Sahara Study Protocol Version: _____
- N-SWEAT Instructions for Use (IFU)
- Case Report Forms (CRFs)
- Subject Information Sheet and Informed Consent (ICF)

In addition, I agree to follow the US Food and Drug Administration (FDA) Regulations, the ethical principles according to the Declaration of Helsinki and The Belmont Report, Good Clinical Practice (GCP) guidelines as applicable (E6 Consolidated Guidance R2) as well as any conditions imposed by the reviewing Institutional Review Board (IRB), US FDA, or other regulatory agency.

Agreed to by (print name): _____

Signature: _____ Date: _____

3. INTRODUCTION AND BACKGROUND

3.1 The Population:

One-third of adults in the United States believe they sweat too much under their arms according to the International Hyperhidrosis Society (IHHS), (Glaser 2018). Based on the 2015 census, this equates to roughly 33 million sufferers in the United States. Many of the people who report heavy sweating have a clinical diagnosis of hyperhidrosis. People with primary hyperhidrosis generally sweat from a certain type of sweat gland called eccrine sweat glands (Strutton 2004, Hornberger 2004). These sweat glands make up the majority of the 2-4 million sweat glands in the human body. Eccrine sweat glands are particularly numerous on the feet, palms, face, and armpit. The prevalence of the condition of hyperhidrosis is reported to be 4.8% in the United States (15.3 million people). Hyperhidrosis is most prevalent in the age 18-39 group (8.8%) and axillae as the most commonly affected area (65%) (Doolittle 2016). Those who sweat excessively report a significant negative impact on quality of life ranging from bothersome to debilitating (Wade 2017, Hamm 2014).

Evidence suggests that the disease of hyperhidrosis is both underreported and underdiagnosed. Data indicate that only about 50% of hyperhidrotic patients discuss their sweating with a physician and, ultimately, only 27% of actual sufferers will be diagnosed with the condition. Many believe that their sweating does not equate to a medical condition and/or that there that there is nothing that can be done to reduce their sweating (Doolittle, 2016). Thus, there is a large population of patients with excessive axillary sweating that could potentially benefit from treatment but have not been diagnosed with primary axillary hyperhidrosis.

This Sahara study is therefore designed to reach all patients with excessive axillary sweating regardless of a diagnosis. Subject will be required to have a Hyperhidrosis Disease Severity Scale (HDSS) Score of 3 or 4 which indicates that sweating is at a level that is considered barely tolerable or intolerable and that sweating frequently or always interferes with the daily life of the patient. This study population will permit the largest and most diverse set of patients and is therefore the most appropriate to confirm the safety and understand the efficacy of the N-SWEAT Patch for the reduction of axillary sweating.

3.2 The Unmet Need:

Currently, the first line of treatment for axillary hyperhidrosis is over-the-counter antiperspirants, while effective for normal sweaters, do not provide an adequate solution for most sufferers and are often irritating. Off-label administration of oral anticholinergic medications and topical application with glyopyrronium wipes typically require daily administration and have unappealing systemic side effects. Currently available in-office procedures (including botulinum toxin injections and use of microwave energy), although effective, can be painful and prohibitively expensive. Moreover, a 2016 IHHS survey showed that even though 87.2% of the 1,985 survey participants had received some form of treatment for their excessive sweating, satisfaction with the treatments received a mean score of “below satisfied” (Glaser 2018). Thus, despite some

currently effective treatments to reduce sweating, there remains a need for additional options to help patients reduce axillary sweating for these patients with an approach that is easy to administer with minimal side effects.

To this end, Candesant Biomedical has developed the CDX-101 Patch, which has been renamed the N-SWEAT Patch. This is a non-invasive topical device designed to reduce sweat production in patients who report heavy sweating in the underarms. The patch is applied in a physician's office to the axillae for up to 3-minutes. During treatment, the patch will generate thermal energy in the presence of sweat and is designed to target the sweat glands for inactivation. After this treatment, the patch is completely removed and disposed of by medical staff.

3.3 Early Evidence for N-SWEAT Patch:

The N-SWEAT patch (previously called the CDX-101 Patch) was studied in a feasibility study in which 12 subjects (both axillae) were successfully treated; 4 of these subjects received an optional (both axillae) retreatment procedure after the initial study period. Thus, a total of 32 Patches were used during this study: 24 in the initial treatments and 8 during the retreatments. Technical feasibility of heat generation was demonstrated across all treatments. The safety endpoint of the study was also met in all patients. There were no serious adverse events (SAEs) reported in the study. Only two (2) device related adverse events were reported; both were deemed mild. Efficacy as measured by a 1-point improvement in HDSS was observed in 91% (11/12) subjects, 64% of the subjects achieved HDSS scores of 1 or 2 at the end of the evaluation period (6-weeks). Mean gravimetric sweat production was reduced an average of 68% across the 6-week follow-up period. QoL survey results showed a consistent trend with the majority of subjects reporting improvement across all measures. Device tolerability was confirmed with all subjects reporting an acceptable level of pain during the procedure.

The outcomes of the STAYDRI.1 Study led the company to the decision to initiate a pilot study with a control group (STAYDRI.A). STAYDRI.A was a prospective, randomized, controlled, double-blinded pilot study, conducted under IRB approval with a non-significant risk designation. Sixteen (16) subjects were successfully randomized (1:1) and treated bilaterally, with both axillae receiving the same treatment; 8 subjects (16 axillae) with the N-SWEAT patch and 8 subjects (16 axillae) with the sham patch. Subjects and evaluating clinicians were blinded to the assigned treatment. The device was shown to be safe with only one (1) device-related AE observed in the N-SWEAT treatment group; the AE was deemed moderate and resolved without sequelae. There were no serious adverse events (SAEs) reported during the study. The efficacy endpoints of the study were also successful. Subjects treated with the N-SWEAT patch demonstrated consistent and sustained improvement in HDSS and additional QoL measurements. A post hoc analysis demonstrated a statistically significant difference in subjects with a 2-point improvement in HDSS between the treated and sham groups, 67% vs 0% respectively at 4-weeks ($p=0.0123$). Further, 83% of treated subjects reported a HDSS score of 1 or 2 at 4-weeks versus 0% in the sham control ($p=0.0032$). Moreover, improvements in both level of "bother" and "impact on daily living" were sustained throughout the study with the difference in QoL scores between the treated and sham groups increasing over the follow-up period. Finally, at the end of the study

(6-weeks) 66.7% of N-SWEAT treated subjects demonstrated a reduction in GSP that was ≥50%. Interestingly, subjects treated with the sham also exhibited a reduction in GSP (mean 44% / median 46%/ ≥50% reduction 14%). It is important to note that subjects treated with the sham did not have corresponding improvements in the QoL assessments as measured by either HDSS or any of the QoL questionnaires. This finding, while on the surface contradictory, is consistent with recent published reports that gravimetric sweat production may not be clinically meaningful in determining the level of disease.

By these two studies, the N-SWEAT device has demonstrated a favorable safety profile. No SAEs have been reported to date. Three (3) total device-related events that occurred in this cumulative data set (2 mild and 1 moderate) were all skin reactions that were treated topically, and all resolved without sequalae. Moreover, data on the subjects' condition after treatment including HDSS and QoL assessments are also consistent; subjects largely feel like their condition is improved.

These findings establish acute safety and suggest effectiveness sufficiently to warrant the initiation of this pivotal trial; the SAHARA Study is intended to confirm safety and further demonstrate efficacy of the N-SWEAT Patch in a larger multi-center representative population.

4. N-SWEAT PATCH INFORMATION

4.1 Indications For Use

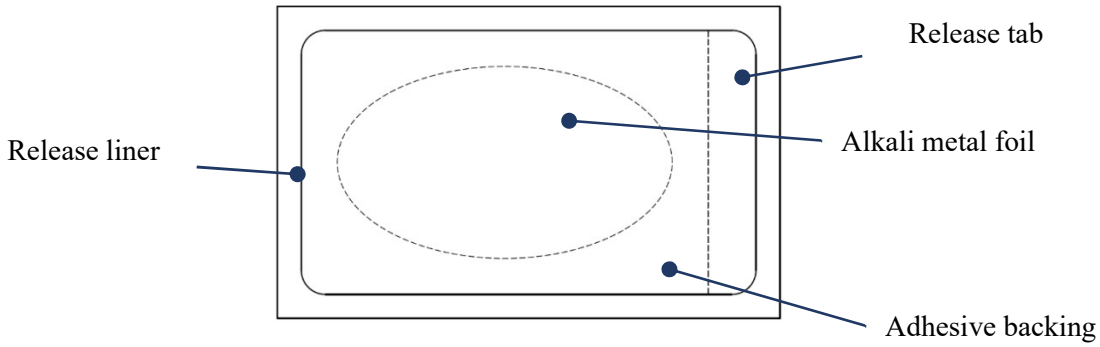
N-SWEAT Patch is indicated for treatment of excessive axillary sweating or primary axillary hyperhidrosis in individuals 22 years of age or older.

The N-SWEAT Patch requires a prescription.

4.2 Description of the N-SWEAT Patch

The N-SWEAT Patch consists of three (3) layers (Figure 1): a thin layer of alkali metal foil (active), an adhesive backing (which helps the patch stay in place during treatment) and a protective barrier layer. The barrier layer protects the patch during storage and is removed and discarded immediately prior to the treatment. The N-SWEAT Patch is single-use.

Figure 1. Diagram of the N-SWEAT Patch



The device is provided non-sterile and is not intended to be sterilized.

There are no accessories, software, or other equipment with the N-SWEAT Patch.

4.3 Mechanism of Action

The N-SWEAT Patch is a non-invasive, topical patch designed to target and temporarily inactivate sweat glands using thermal energy, leading to reduced sweat production.

The N-SWEAT Patch is applied to the surface of dry, unabraded, intact skin by trained clinicians. The patch is activated by water released from sweat glands. When sweat (comprised of up to 99% water, Wilke et al. 2007) comes into contact with the patch, the sodium interacts with the water causing the patch to generate thermal energy. The amount and precise location of heat produced depends on the amount and location of sweat with which the patch comes into contact. In the absence of sweat (water), no thermal energy is generated.

The patch is applied for up to 3 minutes. Removal may occur prior to the 3-minute time point if the patient experiences pain or discomfort (as described in the Instructions for Use (IFU)).

The duration of the effect of the N-SWEAT patch is expected to be 6-8 weeks on average although early clinical data showed some patients maintained reduced sweat at 8-10 weeks. Duration time will be elucidated by this clinical study.

The N-SWEAT Patch is an Investigational Device and is limited by law for use only for subjects enrolled in an approved clinical study.

5. STUDY OBJECTIVE

The primary objective of this study is to evaluate the safety and effectiveness of the N-SWEAT Patch in subjects who experience excessive sweating. The study is designed to confirm device safety shown in previous clinical studies and to demonstrate that the cohort of subjects treated with the N-SWEAT Patch will experience a reduction in sweating relative to sham treated controls.

The study will begin with a roll-in cohort of 10 subjects treated with the N-SWEAT device at one study site. After enrollment into this cohort is complete, adverse event data will be compiled and analyzed. Enrollment into the randomized cohort will commence after these safety data have been reviewed.

This prospective, multi-center, controlled, randomized, blinded, pivotal clinical study is intended to demonstrate sufficient safety and effectiveness of the N-SWEAT Patch for use in subjects with excessive sweating in order to obtain regulatory approval for marketing in the United States and certain other jurisdictions.

6. STUDY ENDPOINTS

6.1 Safety Assessment

Safety will be confirmed by an assessment of the occurrence of local skin reactions, treatment-related AEs and SAEs for all subjects treated with the N-SWEAT device. Local skin reactions are defined by the criteria shown in **Appendix B**. AE and SAEs are defined in **Section 10** of this protocol.

Safety data from the roll-in cohort will be compiled and analyzed after all 10 subjects have completed 2-week and 4-week follow-up. Safety data from the roll-in cohort and the randomized cohort will be pooled.

After the 30th, 60th, and 90th subject from the randomized cohort (active and control) is treated and followed for 7 days, the running safety report will be submitted to FDA. The report will be submitted within 30 days of treatment.

The interval safety report will include:
1. Cumulative frequency tables of all AE reported to date for the active patch, and all the AE reported to date for the sham patch, using the terminology in Table 9; and

2. A list of AEs in the recently completed 30-subject cohort, to include the device used (active or control), time to onset, time to resolution, intervention (including OTC product use), whether the AE was procedure- or device-related, and descriptive and photographic data.

6.2 Primary Efficacy Endpoint

Proportion of subjects in the randomized cohort with Hyperhidrosis Disease Severity Scale (HDSS) of 1 or 2 at the 4-weeks follow-up visit by treatment group. HDSS Scoring is shown in **Appendix A**.

6.3 Secondary Efficacy Endpoints

For sequential hypothesis testing; the primary analysis time point is 4-weeks.

1. Mean improvement in QoL scale Bother by treatment group (randomized cohort)
2. Mean improvement in QoL scale Impact by treatment group (randomized cohort)
3. Proportion of patients with improvement of at least 2 grades from baseline to 4-weeks in HDSS by treatment group (randomized cohort)
4. Proportion of N-SWEAT treated subjects in the randomized cohort with at least 50% improvement in gravimetric sweat production (both axilla combined) (GSP) from baseline to 4-weeks.

All secondary (and primary) endpoints will also be analyzed at all available time points. QoL surveys are included in **Appendix C**. Instructions for GSP measurements are provided in **Appendix D.**

6.4 Observational Endpoints

- Baseline-adjusted mean improvement in QoL-7 instrument assessed by treatment group (randomized cohort)
- Composite - proportion of patients with HDSS 1 or 2 AND 50% improvement in GSP assessed by treatment group (randomized cohort)
- Composite - proportion of patients with HDSS 1 or 2 AND 75% improvement in GSP assessed by treatment group (randomized cohort)
- Duration of efficacy: time from treatment to first observed reversion to HDSS 3 or 4 (median duration of efficacy will be calculated) for all N-SWEAT treated subjects. Also performed for first reversion to subject's baseline HDSS.
- Mean change from baseline over time in GSP compared between treatment groups (randomized cohort); Change in GSP at individual timepoints.

7. SUBJECT POPULATION

7.1 Population Overview

Healthy male and female subjects in good general health who sweat excessively in the axillae and/or who have primary axillary focal hyperhidrosis, defined as subjects with HDSS score of 3 or 4, will be considered for study participation.

The first 10 subjects will be treated with the N-SWEAT Patch and enrolled into the Roll-In Cohort. Subsequently, subjects will be enrolled into the Randomized Cohort and will be randomized for bilateral treatment with either the N-SWEAT Patch or the Sham control patch.

Subjects enrolled in the study will agree to refrain from the use of over-the counter antiperspirants and the use of any topical steroids or any systemic treatment that may impact their hyperhidrosis symptoms during their participation in this study. Subjects will also be required to have axillary hair clipped or shaven prior to GSP assessments at the screening and the 4-week visits.

Subjects will be asked to keep a daily written dairy for the first 4 weeks and to answer weekly surveys related to their axillary sweating; including the HDSS survey and the Quality of Life surveys (QOL-7, QoL-Impact, Bother, etc) using electronic means (i.e. their cell phone, tablet or computer).

The subject will also be required to report for study visits including screening, baseline (on the day of treatment), 2-3 days after treatment, and a 4-week post treatment follow-up visit. Additional visits at 6-, 8-, 10-, and 12-weeks are recommended to take place in person but may be conducted by phone if an office visit is not possible or practical.

Ten (10) subjects will be included in the Roll-In Cohort at 1 study site and up to 110 subjects will be included in the Randomized Cohort at up to 14 study sites. At least 50 subjects randomized to each group must undergo the assigned treatment. Up to 10 additional subjects may be randomized to account for loss to follow up or other missing and critical data.

Candesant intends to enroll a population with demographics representative of the US. Enrollment will be observed to ensure that at least 20% of subjects are Fitzpatrick Skin Types IV through VI and that 10-15% of subjects are Fitzpatrick Skin Types V and VI.

7.2 Eligibility Criteria (Inclusion and Exclusion Criteria)

Subjects considered for enrollment must demonstrate eligibility as outlined below. Documented evidence of eligibility is required and must be housed with the subject's study records.

7.2.1 Inclusion Criteria

The subject must meet **all** of the criteria listed below at the time of enrollment

Table 1. Inclusion Criteria

I-1	Signed written informed consent, including authorization to release health information. (Subject must be able to read informed consent independently since subjective feedback is required)
I-2	Subject is at least 22 years old at the time of consent
I-3	Female or male, who experiences excessive sweating or has been diagnosed with primary focal hyperhidrosis of the axilla and is in otherwise good general health
I-4	GSP >50mg/5min at room temperature/humidity (20-25.6°C/20-80%) at both screening and baseline
I-5	Subject reports a score of HDSS score of 3 or 4 at both screening and baseline
I-6	Subject agrees to avoid use of topical aluminum compounds, antiperspirants, anticholinergic medications or steroids for the duration of study participation
I-7	Subject is willing and able to follow instructions and likely to complete all requirements for the study, including hair removal requirements
I-8	Women of child-bearing age must have a negative pregnancy test at screening and must be practicing and willing to continue an effective method of birth control from screening visit until study completion.

7.2.2 Exclusion Criteria

If any of the following criteria exist, the subject is **not eligible** for participation in the study.

Table 2. Exclusion Criteria

	ELIGIBILITY: EXCLUSION CRITERIA
E-1	Active skin disease, irritation, or abrasions at either axilla based on physical examination by physician at baseline.
E-2	Subject's medical history is indicative of secondary or diffuse hyperhidrosis and/or subject has a diagnosis of secondary or diffuse hyperhidrosis
E-3	GSP exceeds 300 mg/5 min in either axilla at either screening or baseline
E-4	GSP readings differ by more than 100% in either axilla between screening and baseline.
E-5	Hair bearing area of the axillae is more than 6 in length and/or 2.75 in width or is not able to be fully covered by the active (foil) area of one study patch
E-6	Treatment with botulinum toxin for excessive sweating or hyperhidrosis within 1 year
E-7	Undergone any procedures, including for hyperhidrosis, which may affect the axillary areas (e.g., laser hair removal within the last 3 months; or Skoog procedure, any type of sympathectomy, gland excision, or other surgery; thermolysis, liposuction; or iontophoresis) or is planning to undergo any of these procedures during the course of the study
E-8	Use of prescription, prescription strength, or clinical strength topical aluminum compounds for axillary hyperhidrosis (e.g., Maxim, Drysol, Certain Dri) for 30 days prior to screening
E-9	Use of over-the-counter antiperspirants and antiperspirant deodorants for 2 days prior to screening
E-10	Concurrent use of anticholinergic medications (including Qbrexza, glycopyrronium, glycopyrrolate, clonidine, atropine, Bellargal-S), beta blockers, calcium channel blockers, or other topical or systemic treatments that may affect hyperhidrosis symptoms starting at screening visit
E-11	Use of a topical steroid on either of the treatment areas (e.g., hydrocortisone, triamcinolone) within 14 days prior to screening
E-12	Presence of a psychological disorder which may interfere with perception of self or perception of severity of sweating
E13	Use of neuromodulator (e.g. Botox, Dysport, Xeomin) to the hands in the prior 12 months
E-14	Patients with unevaluated lymphadenitis or enlarged lymph nodes should also not be enrolled in case the lymph nodes are reactive or potentially indicative of cancer
E-15	Subjects with allergy to any of the ingredients of the patch
E-16	Patients with conditions or prior treatments in the axilla that may limit the feeling of pain right away or are associated with decreased sensitivity, (e.g. diabetic patients or patients with any other neurological diseases)
E-17	Patients at risk for scarring, collagen vascular diseases, Hidradenitis suppurativa. Patients treated with isotretinoin may also experience severe scarring

7.3 Subject Reimbursement

Subjects that participate in and complete the study visits per protocol will be compensated for their time and contribution. Subject compensation details will be outlined in the site-specific Informed Consent Form (ICF). Payment will only be made for those visits or activities completed. Subjects will not be compensated for missed or incomplete visits, unless extenuating circumstances warrant payment.

7.4 Subject Recruitment

This study may recruit subjects through in-office, online, or other advertising and through existing clients or patients. Any advertising materials to be utilized will be approved by the governing Institutional Review Board (IRB) prior to use.

7.5 Subject Informed Consent

All subjects participating in the Sahara study must provide written informed consent. The investigator or a designated member of his/her staff will approach subjects to obtain this consent and will answer any questions that the subject has. The background of the proposed study and the potential benefits and known risks of the procedures and study will be explained to the subject in a written ICF. The ICF will describe all aspects that are relevant to participation. The ICF will be reviewed and approved by the IRB prior to use.

The subject and the authorized study personnel obtaining informed consent must sign and date the ICF, and a copy must be provided to the subject. Written informed consent must be obtained prior to performing any protocol-driven tests or procedures.

Once written consent has been obtained, the subject will be entered onto a site-specific screening log. All subjects who provide written informed consent will be entered onto the screening log regardless of whether or not they are enrolled into the study.

A legally authorized representative will not be permitted to provide consent on behalf of study subjects in the Sahara Study. The subject must be able to provide active feedback on tolerability during the treatment and must be able to read independently in order to provide accurate and subjective feedback during follow-up surveys.

8. PROCEDURES AND ASSESSMENTS

8.1 Initial Screening

Prior to obtaining written informed consent, the subject's existing medical (or other clinic) records may be reviewed to determine whether or not the subject might be an acceptable candidate for the Sahara Study. If initial review indicates that the subject may be eligible, the subject may be approached regarding the study, and the informed consent process may commence.

Once the subject has provided consent, a screening visit may be scheduled to conduct final screening assessments. Note that requirements for cessation of other treatments may require a lead time for scheduling this visit.

8.2 Active Screening

Active study screening will begin at a screening visit. Assessments conducted at this visit will include the following:

- **History and Demographics:** General inclusion and exclusion criteria review and health evaluation to ensure that the subject is not planning to undergo a surgical procedure during their expected participation in the study, is not actively participating in another clinical study that may confound the results of this study, and is willing to comply with the requirements should be conducted first. Only after these qualifications are met; should the following 2 assessments (GSP and HDSS) be conducted.
    - *NOTE: If excessive hair is present on the axilla at the screening visit the hair shall be clipped or shaven during this visit prior to conducting assessments. Stubble or minimal hair is acceptable.*

- **GSP**: Gravimetric sweat production should be measured in accordance with instructions and training provided by the sponsor (**Appendix D**). Any deviation from this procedure should be documented and explained. In summary, measurements will be obtained following a period of rest in normal room temperature. Subjects will have a pre-weighed filter paper placed in each of their axillae for 5 minutes. The difference in the filter paper's weight before and after will be considered the GSP measurement.
    - At the baseline, the GSP assessment is required to show at least 50 mg/5 min of spontaneous resting axillary sweat production in each axilla and no more than 300 mg/5 min in either axilla.

- **HDSS**: The Hyperhidrosis Disease Severity Scale should be explained to the subject in plain language and in accordance with the instructions and training provided by the sponsor (**Appendix A**). It should be clear to the subject that they are answering these questions to report on their underarm sweating. The subject will be asked to take this test weekly throughout the study via questionnaire that will be sent electronically by cell phone, tablet, or computer.
    - At the baseline visit, Subject HDSS score be 3 or 4

- **Pregnancy Test**: Women of child-bearing potential with no history of hysterectomy are required to have a negative pregnancy test and must be practicing and willing to continue using an effective method of birth control from screening visit until study completion.

- **Assessment for Local Skin Reactions***:* The investigator will evaluate axillary application sites for any skin irritation. If present (greater than 1) based on the Skin Erythema Assessment and the Clinical Signs/Symptom Descriptors (**Appendix B**), the subject may only be treated once the issue has been resolved (less than or equal to 1).

Once the subject has completed these initial assessments and has been deemed eligible, the subject will be scheduled to report back for baseline assessment and potential Treatment. The baseline/treatment assessment must be scheduled at least 72 hours after any hair removal. All subjects should be provided with clear instructions that no shaving or clipping shall be conducted within 72 hours of the scheduled baseline/treatment visit. The presence of stubble is acceptable.

An approved deodorant (without antiperspirant) will be provided to all eligible subjects at the conclusion of this visit; this deodorant should be used by the subject starting at the screening visit through the duration of their participation in the study. If the subject wishes to use a different deodorant; it must be approved by the sponsor.

8.3 Baseline Assessment

8.3.1 Prior to Enrollment

No more than 14 days after the screening visit the subject will report for baseline assessment and potential treatment. (*NOTE: If axillary hair was clipped at the screening visit, the baseline visit must be at least 72 hours later*). All efforts should be taken to make sure that the subject is prepared to undergo treatment during this visit if they meet the eligibility requirements below.

Baseline Assessments include:

- **GSP**: Gravimetric sweat production should be measured in accordance with the instructions and training provided by the sponsor (**Appendix D**). Any deviation from this procedure should be documented and explained.
    - At baseline, subject GSP assessment is required to show at least 50 mg /5min of spontaneous resting axillary sweat production in each axilla and no more than 300 mg/5 min in either axilla. The difference between screening and baseline for either axilla may not be >100%.

- **HDSS**: The Hyperhidrosis Disease Severity Scale should be explained to the subject in plain language and in accordance with the instructions and training provided by the sponsor (**Appendix A**). It must be clear that these questions relate to underarm sweating.
    - Subject HDSS score must be 3 or 4

- **Physical Exam**: The subject must be in good general health and able to independently assess their sweating in a reasonable way.
- **Assessment for Local Skin Reactions***:* The investigator will evaluate axillary application sites for any skin irritation. If present (greater than 1) based on the Skin Erythema Assessment and the Clinical Signs/Symptom Descriptors (**Appendix B**), the subject may only be treated after the issue has been resolved (less than or equal to 1).
    - **NOTE**: *If abrasions or broken skin are present; the subject may report back for re-screening after the skin has had time to heal (at least 72 hours). Treatment in the study in the presence of skin irritations or abrasions can lead to increased probability of the patient experiencing discomfort, pain or skin irritations.*
    - **NOTE:** The subject must meet the criteria above in both axilla since the study treatment includes treatment of both axillae in the same procedure.

Once the subject has completed these assessments and has been deemed eligible, the subject can be treated as party of either the Roll-In Cohort or the Randomized Cohort and will be considered enrolled as described below. All efforts should be taken for treatment to occur on the same day. If the subject is not able to have treatment on the same day as the baseline visit and is in the Randomized Cohort, randomization should not take place. Randomization should occur immediately before treatment.

8.3.2 After Confirmation of Eligibility

The Quality of Life (QoL) questionnaires should be completed by the patient to establish the baseline condition. QOL surveys will include: QOL-7, which has a total of 7 questions, QOL (Bother and Impact) which has 2 questions total and an additional survey with up to 5 QoL assessment questions may be included to collect informative data on the patient population. If possible, the subject should complete these surveys electronically.

8.4 Roll-In Cohort

Subjects in this cohort are enrolled once they undergo treatment with the N-SWEAT Patch.

8.5 Randomization Cohort

8.5.1 Randomization Process

Note: Randomization should take place immediately before treatment. If a subject meets all eligibility criteria at the screening and baseline visits; but is unable or unwilling to undergo treatment. Do not randomize. The subject should report back for randomization at the time of their planned treatment. If it is more than 7 days

between the qualifying baseline visit and randomization; the HDSS and the physical exam should be repeated to confirm eligibility prior to Randomization.

Randomization will be performed using an electronic system. Upon entering the subject information, the electronic system will assign a unique treatment to the subject. The subject must be treated with the assigned treatment number. In the event that the site is prevented from using the assigned treatment number (either due to the patch being missing, damaged or otherwise unusable) the site must contact the sponsor to receive an alternate treatment number assignment. A contact list will be provided for this purpose.

Subjects will be randomized 1:1 to either an active study N-SWEAT Patch (Treatment) or a sham patch (Sham). There will be no procedural difference between the Treatment Arm and the Sham Arm. The randomization will be stratified by HDSS 3 vs. 4 at baseline and blocked by investigational center. Within each HDSS stratum, block randomization with a randomly selected block size will be used. Up to 110 subjects will be randomized. At least 50 subjects randomized to each group must be evaluable for the primary efficacy endpoint. Up to 10 additional subjects may be enrolled to account for loss to follow up or other missing and critical data.

Crossovers are not permitted by this protocol. Subjects may only receive the N-SWEAT Patch if they are randomized to do so.

8.5.2 Blinding

Subjects in the randomized cohort will be blinded to the Study Arm to which they are randomized.

Site personnel will not be informed of the specific Study Arm assignment (they will only know the treatment # assigned); those administering the treatment will observe the treatment effect and the disposal process and may be unblinded as a result of their observations. This person will not conduct the follow-up assessments. These personnel will be instructed and trained not to reveal the assumed Study Arm assignment to any subject or to any of the other study personnel at the site. Site personnel completing follow-up evaluations will be different from the person who conducted the procedure and, therefore, will be blinded to the subject's treatment.

Subjects will be instructed (by subject handout Appendix G) not to discuss their assumed treatment assignment with anyone at the study site.

Only necessary persons at the sponsor shall know the treatment assignments and only those persons will have access to the database which holds the key for the treatment numbers distributed at each site. All others at the sponsor will remain blinded.

8.6 Enrollment

As described above, subjects will be considered enrolled if they have given informed consent, they meet the study eligibility criteria upon assessment at both screening and baseline, and they are treated as part of the Roll-In Cohort or undergo randomization. A schematic overview of the subject enrollment process is shown in **Figure 2**.

Enrolled subject will be entered into the study database. Upon entering the subject into the study database, a unique subject ID will be assigned to the subject by the electronic system.

The unique subject ID that is assigned will be based upon the information entered by the study site. In summary, the subject ID will be assigned as follows: Sahara study identifier (SAH), followed by the 3-digit site ID (XXX), a 3-digit unique subject ID (a consecutive number determined by the electronic system from the number of patients enrolled at the time the subject is added), followed by the subjects initials (YY) (defined as first letter of first name then first letter of last name), i.e., SAH-XXX-001YY, SAH-XXX-002YY, etc.

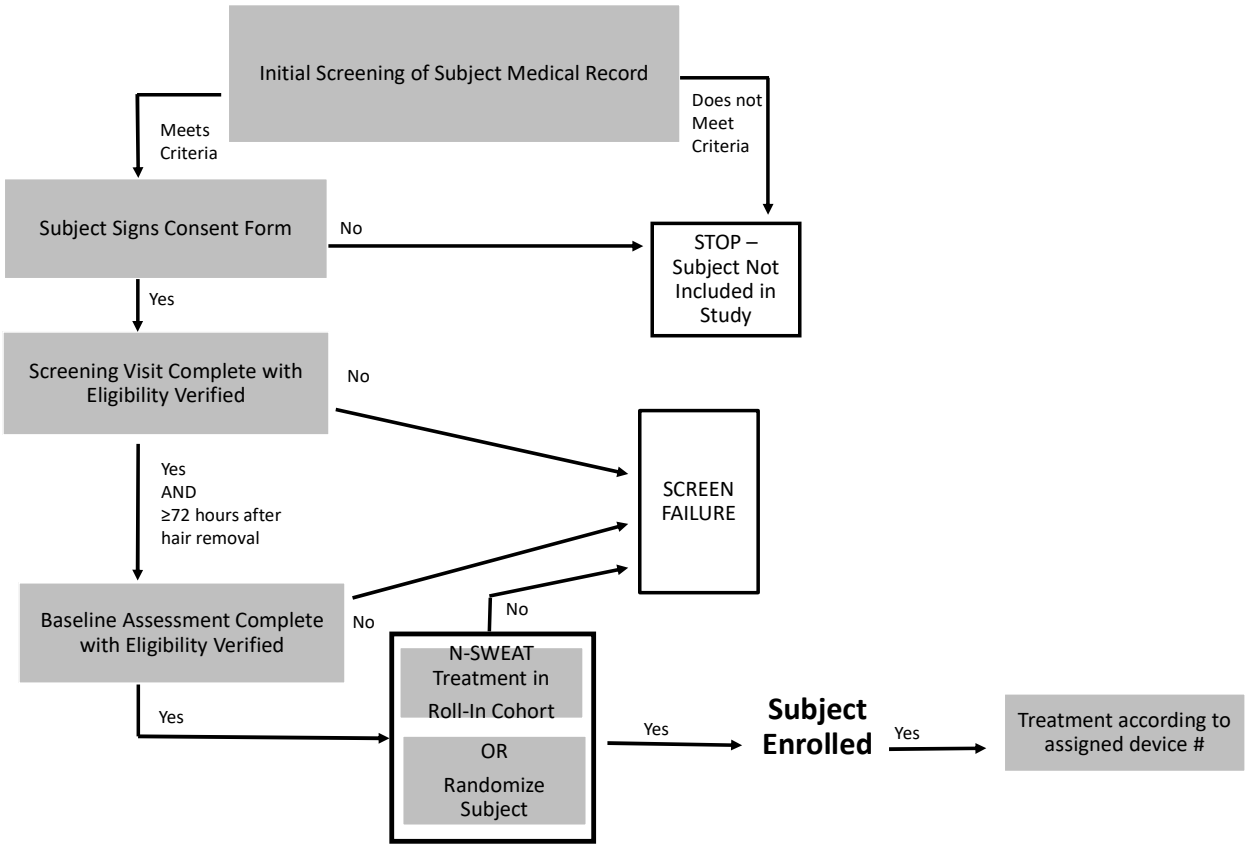
Once the subject is added and the unique subject ID is assigned, the subject will be automatically assigned to the roll-in cohort, or, randomized and assigned a treatment number as explained above.

The site will maintain a Subject Screening Log, which will link the unique subject ID to the subject. This log will remain confidential and will not be provided to the sponsor, but, will only be used for reference during monitoring at the study site.

8.6.1 Screen Failures

If the subject has consented, but becomes ineligible prior to enrollment, the reason for ineligibility will be documented on the Screening Log. A copy of the subject's consent will be maintained in the site's study records. Ineligibility may occur at the screening visit, at the baseline visit or prior to randomization. Once a subject is randomized; they are enrolled. Treatment with the assigned treatment number should be conducted.

Figure 2: Enrollment Flowchart, Initial Screening through Treatment



8.7 Procedure

The Candesant N-SWEAT Patch is intended for use only by appropriately trained personnel. All investigators and support staff will be provided comprehensive training by Candesant Biomedical (or their designee) in the handling, use, and disposal of the patch. Treatment will be performed in a clinic or doctor's office, by a trained medical professional.

8.7.1 Immediately Pre-Treatment

The following baseline evaluations will be performed immediately prior to treatment, in the following order.

Treatment Site Identification: The target treatment area should be chosen by identifying a relatively flat area with the highest concentration of hair follicles. This placement is intended to maximize contact with the location of sweat production. The planned treatment site may be marked for convenience.

Treatment Site Assessment: Although an assessment should have been conducted prior to randomization; the planned treatment area(s) should be inspected a final time to ensure the planned site meets treatment requirements as outlined in the N-SWEAT Patch Instructions for use (IFU). The area must be free of residue, and free of

abrasions, broken skin, or other conditions of concern. The assessment should include both visual and tactile assessment of any irregularities.

> **Note**: *Areas with skin tags, moles or other skin abnormalities that are not indicative of abraded skin are permissible for treatment. At the discretion of the treating physician the area may be avoided with strategic patch placement and/or use of an adhesive strip.*
>
> **Note**: *If skin irritation is noted, it should be assessed in accordance with the Erythema and Clinical Signs/Symptoms (**Appendix B**). If irritation greater than 1 is observed,* the subject may only be treated after the issue has been resolved (less than or equal to 1).

Hair removal by clipping or shaving should NOT be done within 72 hours prior to the procedure. If the planned area does not meet the IFU requirements, do not proceed with treatment. If the operator has questions or concerns regarding the treatment site, the sponsor should be contacted for consultation before moving forward with the procedure.

Treatment Site Preparation: The subject's axilla will be cleaned with alcohol to ensure that no residual deodorant / anti-perspirent or other residue remains in the target treatment area. The area shall then be thoroughly dried.

Photos: Pre-treatment photos are to be taken of each axilla and maintained by the study site as a baseline reference in the event that an adverse skin reaction should occur or another matter necessitating review for patient safety. Photos are to be taken with a high-resolution camera with the arm in the standardized treatment position and adequately illuminated. Photos are to be marked with Subject ID, date and subject side (i.e. Right or Left). Photos are to be taken with a measurement calibration reference visible.

8.7.2 Patch Application

An overview of the patch appplication procedure is provided below; however, it is critical to reference the IFU provided for additional treatment and handling details.

Per the IFU, all personnel involved in the handling of the provided patch must have gloved hands at all times.

The patch will be placed on the target treatment area (as previously described). If the subject reports any pain or uncomfortable sensation at the time of patch placement; the patch should be immediately removed.

Upon placement of the patch, the timer shall be started. Every 30 seconds, the subject shall report their pain level on a score of 1 to 10. If the subject reports a pain level greater than 8 or shows a 8 or higher using the Wong-Baker FACES pain scale (**Figure 3**); the patch should be removed immediately regardless of the time that the patch has been in place.

Figure 3. Wong-Baker FACES® Pain Rating Scale

If the timer reaches 3 minutes and the patch is still in place, it should be removed at the 3 minute mark. The actual treatment duration should be documented in the subject's study record. The procedure may be photographed or videotaped (provided the subject has consented to video/photography). The subject's identity will be concealed, and subject confidentiality will be maintained at all times.

NOTE: In the event of excessive exposure to the N-SWEAT patch or insufficient cleaning post treatment, an alkaline or thermal burn is possible. Acute burns are treated by flushing with water for 30 minutes followed by routine skin and wound care (Sander, 2011). Please have water and gauze available at all times when using the N-SWEAT patch.
Please refer to Appendix G for guidance on when to refer to a burn center.

8.7.3 Immediately Post-Treatment

Immediately following patch removal, the treatment area will be thoroughly cleansed with water. A gauze pad soaked with water should be used to wipe the area a few times. This step should be repeated until the subject does not feel any residual effects, such as tingling or stinging. The subject should be asked to report their pain level using the Wong-Baker FACES pain scale during cleaning. The treatment area will be visually assessed by the physician, photographs may be taken, and any noted Adverse Events (AEs) will be documented.

Assessment for Local Skin Reactions*:* The investigator will evaluate axillary application sites for skin irritation to determine if there is an immediate reaction to the investigational device. If present it should be documented in accordance with the Skin Erythema Assessment and the Clinical Signs/Symptom Descriptors (**Appendix B**).

8.7.4 Treatment of the Second Axilla

All steps (8.7.1 through 8.7.3) above will be repeated for treatment of the second axilla in the same treatment visit.

8.7.5 Subject Care and Medications

Subjects will be provided with instructions for post-treatment care. They will be instructed to rinse the area with water or cleanse with soap and water if they feel any discomfort. Deodorant will be provided for use during study participation.

Subjects may take over-the-counter pain medication as needed following treatment. Acetaminophen is recommended for pain control. Prescription strength pain medication is not expected to be necessary.

Subjects must refrain from using over-the-counter or prescription, prescription-strength, or clinical strength topical aluminum compounds or antiperspirants for the duration of study participation. An approved deodorant (without antiperspirant) will be provided at screening for convenience. Other deodorants without antiperspirant may be allowed; however, they must be approved by the investigator. Subjects must also refrain from using topical steroids or hair removal creams on the treatment areas.

Subjects must refrain from taking anticholinergic medications, beta blockers, calcium channel blockers, other systemic treatments, or medications that are known to cause heavy sweating during the study. If one or more of these medications or treatments are required, and in the opinion of the investigator would compromise study results, the subject will be followed for safety only. All relevant medications taken will be documented.

8.8 Follow-up Evaluations

Subjects will undergo phone evaluations at 24 hours (± 12 hours) and 2-weeks (±2 days) following treatment, at which time subjects will be asked about their discomfort and if they may have experienced an AE. If the subject has symptoms, a telehealth or clinical visit should be scheduled to assess the subject's condition within 24 hours. Any concern for burn injury should result in an in-person clinic visit. Please refer to Appendix G for conditions under which subjects should be referred to the burn center.

A follow-up visit is required at 48-72 hours post-treatment. Visit will include a physical exam, assessment of vitals, and treatment site assessment. Any new treatment area symptoms should result in a telehealth or clinic visit being scheduled (within 24 hours) to assess the subject's conditions. Any concern for burn injury should result in an in-person clinic visit. In addition, a written daily dairy will be provided to subjects to record treatment site pain or other symptoms.

Beginning 1-week post treatment, the subject will be asked to complete the HDSS and QoL surveys electronically once per week. The survey may be taken electronically via cell phone, tablet or computer. The subject will receive instructions at the baseline visit. Subject will be reminded to complete the surveys via text or email, per their preference. In the event that the electronic submission is not possible, the subject will be asked to complete the surveys on paper and mail it to the clinic. If a subject fails to complete the survey in a timely matter the site will be notified so that they can make contact with the study subject.

Subjects will be asked to schedule follow-up evaluations at 2-week intervals starting on 4-weeks (i.e. 4-, 6-, 8-, 10-, and 12-weeks post-treatment). However**, the 4-week visit is required to take place as an office visit**. The rest of the visits are recommended to take place in person but may be conducted by phone if an office visit is not possible or

practical. If at any time, the subject reports local skin reaction or an adverse event, a clinic visit should be scheduled for direct assessment by the study medical team.

When possible, subjects are to undergo follow-up visit evaluations at the same time of day of the week and around the same time of day as their baseline evaluations. In the event that the subject is not able to report on the same day as the baseline evaluations, the visit window permits the subject to report up to 1-3 days earlier or later than the target weekday. The visit windows are shown in **Table 3** below.

Table 3. Visit Windows

Visit	Window
24-hour phone call	± 12 hours
48-72 hour visit	± 1 day
2-week phone call	± 2 days
4-week, 6-week, 8-week, 10-week, 12-week visits	± 3 days

Follow-up evaluations to be conducted at follow-up visits are summarized below in **Table 4**.

Table 4. Follow-Up Assessments

Assessment	Time	Method	Reference
Daily Diary	Daily through 4-weeks	Written journal returned at 4-week visit	Appendix F
HDSS	Weekly	Visit or electronic	Appendix A
QoL Assessments	Weekly	Visit or electronic	Appendix C
Assessment for Local Skin Reactions	Immediately post treatment, AND, at every clinic visit	Visit required	Appendix B
GSP*	**4-weeks ONLY**	Visit required	Appendix D

**NOTE: If excess hair is present on the axilla at the 4-week visit, the hair shall be clipped prior to conducting GSP testing. Stubble or minimal hair is acceptable. GSP should be measured in accordance with the instructions and training provided by the sponsor. Any deviation from this procedure should be documented and explained.*

Table 5 summarizes the subject schedule for the study.

8.9 Extended Follow-Up Cohort

An important outcome to be assessed by the Sahara Study is the duration of the effect of the N-SWEAT Patch Treatment. Therefore, subjects that reach the final Sahara Study visit (12 weeks) and are still responding to treatment (i.e. HDSS has not returned to Baseline) will be invited to continue follow-up by enrollment into an Extended Follow-Up Cohort. Eligible subjects will provide consent prior to being enrolled into this cohort, within 4 weeks of completing their 12-week visit.

Subjects enrolled in this cohort will not undergo any additional treatment, their participation will include extended follow-up only through 24-weeks post treatment or when HDSS returns to Baseline (whichever occurs first)

Subjects enrolled into the Extended Follow-Up Cohort will be asked to continue weekly electronic surveys until participation is complete. Phone Calls shall be scheduled with subjects in this cohort by the site study team at 16-weeks, 20-weeks and 24-weeks post treatment during participation.

Table 5. Subject Visit Schedule

	Screening	Baseline	24 hours	48-72 hours	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
			±12 hrs	*±1 day*	*± 2 days*		*All other follow-up visits window include ± 3 days*									
Clinical Visit Required	X	X		X				X								
Clinical Evaluation (Visit Recommended)										X		X		X		X
Clinical Evaluation **(Phone Call Required, Visit if symptomatic**)			X			X										
Daily Diary				Daily completion through 4-week visit												
ELECTRONIC ASSESSMENTS (cell phone, tablet, computer)																
HDSS					X	X	X	X	X	X	X	X	X	X	X	X
QoL-7		X			X	X	X	X	X	X	X	X	X	X	X	X
QoL (Bother and Impact)		X			X	X	X	X	X	X	X	X	X	X	X	X
Additional QoL Assessments		X			X	X	X	X	X	X	X	X	X	X	X	X
HDSS by Site	X	X														
GSP	X	X						X								
Assessment for Local Skin Reactions	X	X						X[1]		X[1]		X[1]		X[1]		X[1]
Physical Exam	X	X						X[1]		X[1]		X[1]		X[1]		X[1]
Pregnancy Test *(for women of child-bearing potential ONLY)*	X															
Assessment for AEs since last visit			X					X		X		X		X		X

[1] *To be conducted at all clinic visits*

8.10 Study Exit or Premature Withdrawal

Subjects will be formally exited from the study through the completion of the Study Exit CRF at the time of study completion, provided the subject has not experienced an AE directly attributable to the study device or procedure that is ongoing and unstable and/or unexplained.

Subjects may be prematurely terminated or withdrawn from the study for the following reasons:

- Not eligible for treatment
- Subject starts a medication or treatment that, in the opinion of the investigator, may skew study results
- Lost to follow-up (following 3 documented attempts to reach subject)
- In the investigator's opinion, it is not in the best interest of the subject to continue study participation
- Voluntary withdrawal, meaning that the subject voluntarily chooses not to participate in the study

All subjects enrolled (including those prematurely withdrawn) shall be accounted for and documented.

9. STATISTICAL METHODS

9.1 General Statistical Analysis Methods

Categorical variables will be summarized by counts and percentages. Continuous variables will be summarized by n, mean, standard deviation, minimum, median and maximum.

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

9.2 Study Design, Randomization and Blinding

The Sahara Study is a prospective, multi-center, randomized, blinded, pivotal study to evaluate the safety and effectiveness of the N-SWEAT Patch.

Subjects with primary axillary hyperhidrosis or excessive sweating (defined by a score of 3 or 4 on the HDSS), who have provided informed consent and have met the study eligibility criteria, will participate. Up to 120 adult subjects will be enrolled. The first 10 subjects will be treated with the N-SWEAT patch and constitute the roll-in cohort and up to 110 subjects will be randomized to 1 of 2 treatment groups in a 1:1 ratio to receive a single administration of the N-SWEAT Patch or a sham control patch. The randomization will be blocked by investigational center and stratified by HDSS 3 vs. 4 at baseline. Up to 10 additional subjects may be enrolled to account for loss to follow up or other missing and critical data.

Randomized subjects will be blinded to their treatment assignment. Site personnel administering the treatment will observe the treatment effect and the disposal process and may be unblinded as a result of their observations. This person will not conduct the follow-up assessments and will not reveal the assumed treatment assignment to the subject, other site personnel, or the investigator at any time during the study follow-up period. Study subjects and study staff will be instructed not to discuss assumptions about the treatment received.

The sponsor will identify those who need to be unblinded in order to conduct the study. All others at the sponsor will remain blinded.

9.3 Sample Size and Power Considerations

The primary effectiveness evaluation is driving the randomized sample size for the trial. The maximum of two scenarios considered required 50 evaluable per randomized group at 4 weeks of follow-up. Increasing that number for up to 10% attrition requires 55 randomized subjects per group or 110 randomized subjects. This number provides at least 80% power for the primary efficacy objective.

The trial is also designed to also enroll a roll-in cohort of N=10 treatment subjects at one investigational center prior to randomizing any subjects in the trial.

9.4 Study Success

The Sahara study will be deemed a success with a statistically significantly higher proportion of patients with HDSS score of 1 or 2 at 4 weeks post-treatment in subjects randomized to treatment vs. sham (primary effectiveness endpoint) accompanied by an acceptable safety profile.

9.5 Analysis Sets / Populations

9.5.1 Roll-in Cohort

The roll-in cohort is an initial cohort of N=10 treatment subjects enrolled at one investigational site to provide FDA with an initial assessment for safety of the device. Efficacy endpoints for roll-in subjects will be restricted to summary statistics and reported separately for roll-in subjects.

9.5.2 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized patients assigned to treatment. In this population, treatment will be based on the treatment to which patients were randomly assigned regardless of which treatment they actually received.

9.5.3 Safety Population

The safety population is the ITT population plus the roll-in cohort.

9.5.4 Modified Intent-to-Treat and Full Analysis Set

The modified intent to treat (mITT) will include all randomized patients in the ITT population who were exposed to randomized treatment. The full-analysis set (FAS) is those mITT subjects that have evaluable data for the endpoint.

The mITT population, like the ITT population, will include all randomized patients assigned to treatment regardless of which treatment they actually received. However, unlike the ITT population, the mITT population excludes patients who are randomized but fail to initiate treatment (treatment or control patch).

9.5.5 Per-Protocol Set

The Per Protocol Set (PP) will include all randomized subjects in the FAS who did not have any major protocol violations. Definitions of major and minor protocol violations will be included in the Statistical Analysis Plan (SAP) prior to data lock and unblinding of the person(s) determining major or minor status. If no subjects are excluded from the PP, the PP will not be required. The PP will be used for supporting analyses of efficacy data.

9.6 Timing of Analyses

Safety for the Roll-in cohort will be summarized when at least 2 weeks of follow-up is available on the last enrolled roll-in subject.

Once all subjects complete 4 weeks of follow-up, the data will be summarized for evaluation of the endpoints. Lastly, the data will be summarized when all subjects complete 12 weeks of follow-up.

9.7 Assessment of Comparability of Randomized Groups and Evaluation for Pooling

9.7.1 Demographics / Baseline Characteristics and Protocol Administration

Patient disposition will be listed and summarized for the mITT, ITT and roll-in data sets by treatment group. Protocol deviations will be collected and summarized by randomized group in the ITT population and roll-in group.

Demographics (age, gender, race/ethnicity) and baseline characteristics (HDSS, GSP, Fitzpatrick skin type, and BMI) will be summarized by treatment group for ITT, mITT and roll-in groups.

The randomized groups will be compared at time of randomization for the important demographics and baseline characteristics specified. Should additional important baseline parameters be identified prior to the analysis, they will be evaluated in the same manner. Any of the variables that are significant at a two-sided □=0.05 will be evaluated as covariates or strata variables in the primary effectiveness analysis or as an additional or supporting analysis to the primary effectiveness endpoint and if desired, secondary/observational endpoints as well. Continuous variables will be evaluated both as stratification variables by dichotomizing the subjects into two groups based on the median or other appropriate value and as a continuous variable in the statistical models. Logistic regression analysis may be used for the primary efficacy endpoint should it be desirable to evaluate multiple covariates simultaneously in a statistical model.

9.7.2 Treatment Characteristics

At a minimum, the duration of patch placement, pain level during treatment and cleaning will be summarized by randomized group for the mITT and roll-in population.

9.7.3 Evaluation for Pooling

Pooling of the investigational sites will be evaluated for the primary efficacy endpoint. Investigational centers with less than 10 randomized subjects will be combined for this purpose. The Breslow-Day test will be used to assess the treatment by site interaction and if statistically significant at $p<0.15$, an overall response rate will be evaluated at 4-weeks using CMH test stratified by site. If not statistically significant, the data will be pooled for analysis.

9.8 Handling of Missing Data for the Primary Efficacy Endpoint

A sensitivity analysis to the missing data in the mITT sample will be conducted for the primary efficacy endpoint. The sensitivity analysis will include a best case, worst case and tipping point analysis. The best case analysis will impute successes for subjects randomized to treatment with missing data and failures for subjects randomized to sham with missing data. The worst case analysis will impute failures for subjects randomized to treatment with missing data and success for subjects randomized to sham with missing data. The tipping point analysis completes the matrix of imputations possible between the best case and worst analysis to determine where statistical significance is maintained or lost. If the worst case analysis maintains statistical significance, the tipping point analysis is not necessary.

9.9 Primary Safety Analysis

Subjects Included in Analysis: All subjects in the Safety Cohort.

Endpoint(s): Local skin reactions and adverse events.

Hypothesis: A single hypothesis test associated with a specific safety endpoint is not being proposed for the primary safety outcome. Rather, the local skin reaction and adverse event profile in total will be reviewed for acceptability.

Primary Statistical Analysis: Number and percent of subjects affected by each event or reaction will be summarized. Subgroups of events/reactions will also be summarized and include but are not limited to serious events, those related to the treatment, and those that are both serious and related to the treatment.

9.10 Efficacy Analysis

9.10.1 Primary Efficacy

The proportion of subjects with HDSS of 1 or 2 at 4-weeks in subjects randomized to treatment (p_T) will be higher than that in subjects randomized to sham (p_S).

Subjects Included in Analysis: All mITT subjects.

Endpoint(s): The proportion of subjects with HDSS of 1 or 2 at 4 weeks of follow-up.

Hypothesis*:*

H_o*:* The proportion of subjects with HDSS of 1 or 2 at 4-weeks in subjects randomized to treatment (p_T) will be lower than or equal to that in subjects randomized to sham (p_S), $p_T \leq p_S$

H_a*:* The proportion of subjects with HDSS of 1 or 2 at 4-weeks in subjects randomized to treatment (p_T) will be greater than that in subjects randomized to sham (p_S), $p_T > p_S$

Sample Size Rationale: . The sample size and power calculations for the randomized cohort are based on the company's clinical trial data as well as on published data (Glaser et al., 2012). To account for substantial variability in the proportion of responders across various trials, multiple scenarios were considered.

Per definition of the primary endpoint a responder is a patient with HDSS values of 1 or 2 at 4-weeks post treatment. If proportions of responders in the treated vs. sham arms are 85% vs. 60%, respectively, then using PASS 2019, testing two proportions using the Mantel-Haenszel test, 50 patients per arm will be needed to detect the treatment difference with the 80% power at the 0.05 two-sided significance level. If proportions of responders in the treated vs. sham arms are 73% vs. 44%, then 45 patients per arm will be needed. The evaluable sample size of 50 patients per arm was chosen

Primary Statistical Analysis*:* The proportion of patients with HDSS of 1 or 2 at 4 weeks post-treatment will be compared between treatment vs. sham using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HDSS value of 3 vs. 4 in the FAS population. Statistical significance is achieved with two-sided p-value <0.05 equivalent to one-sided p-value < 0.025.

Additional Statistical Analysis: Additional analyses include those summarized in Section 9.7.3 Evaluation for Pooling of Data and Section 9.8 Handling of Missing Data for the Primary Efficacy Endpoint. The primary statistical analysis will be completed in the PP population as well.

An analysis will also be performed using all available time points with complete follow-up at the time of the analysis. A generalized linear mixed model be used to compare the proportion of subjects with HDSS of 1 or 2 between randomized groups over time on study. The dependent variable is HDSS of 1 or 2 (Y/N) with independent variables to include randomized group, follow-up time, baseline HDSS and two-way interaction terms. The covariance structure among the compound symmetric, auto-regressive and unstructured that provides the best model fit by the Schwarz BIC criterion will be used.

A hierarchical stepwise backward elimination technique will be used to reduce the model. The two-way interactions will be reviewed first, the two-way interaction with the largest p-value provided that p-value is greater than 0.05 will be removed from the model and the model refit and process repeated until only two-way interactions with p-values < 0.05 are retained. The main effects for any two-way interactions retained in the model must remain in the model as well as the randomized treatment. With that said, the main effects will be evaluated in the same manner as two-way interactions. This analysis will be repeated in the PP population as well.

9.10.2 Secondary Efficacy

9.10.2.1 Type I Error Control, Additional Claims and Labeling

Should the primary effectiveness endpoint be found to be statistically significant, additional secondary endpoints will be evaluated for inclusion in the labeling for the device including p-values and 95% confidence intervals. The secondary endpoints listed in Section 9.10.2.2 are in priority order and will be evaluated in that order. If statistical significance is achieved for the highest priority endpoint the testing will move to the next highest until either statistical significance is not reached, or the list has ended. This ordered hypothesis approach permits each hypothesis to be evaluated at two sided α=0.05 or equivalently one-side □=0.025 and controls the study-wide Type I error at 5%.

Secondary endpoints or additional analysis outside of those that do support additional claims are supportive in nature and not intended to support additional claims. Data may be included in labelling per agreement with the FDA and will be limited to summary statistics (e.g. mean, standard deviation, minimum, median, maximum, number and percent) and will not include 95% confidence intervals or p-values. For more information about the secondary endpoint analyses see Section 9.10.2.3 Secondary Objectives.

9.10.2.2 Priority Order and Hypothesis Tests

These hypothesis tests will be evaluated in the FAS population.

1. **To prove that the mean improvement in QoL scale Bother from baseline to 4-weeks is statistically significantly greater in the treatment group as compared to the sham group.**

***Hypothesis**:*

H_o*:* The mean improvement in QoL scale Bother from baseline to 4-weeks in subjects randomized to treatment (μ_T) will be lower than or equal to that in subjects randomized to sham (μ_S), (μ_T) ≤ μ_S.

H_a*:* The mean improvement in QoL scale Bother from baseline to 4-weeks in subjects randomized to treatment (μ_T) will be greater than that in subjects randomized to sham (μ_S), $\mu_T > \mu_S$.

Success is defined as a statistically significant difference (at the 0.05 two-sided significance level) between least squared means for randomized groups.

2. **To prove that the mean improvement in QoL scale Impact from baseline to 4-weeks is statistically significantly greater in the treatment group as compared to the sham group.**

***Hypothesis**:*

H_o: The mean improvement in QoL scale Impact from baseline to 4-weeks in subjects randomized to treatment (μ_T) will be lower than or equal to that in subjects randomized to sham (μ_S), $\mu_T \leq \mu_S$

H_a: The mean improvement in QoL scale Impact from baseline to 4-weeks in subjects randomized to treatment (μ_T) will be greater than that in subjects randomized to sham (μ_S), $\mu_T >$ □$_S$

Success is defined as a statistically significant difference (at the 0.05 two-sided significance level) between least squared means for randomized groups.

3. **To prove that the proportion of patients with improvement of at least 2 grades from baseline to 4-weeks in HDSS is statistically significantly greater in the treatment group as compared to the sham group.**

***Hypothesis**:*

H_o: The proportion of subjects with improvement of at least 2 grades from baseline to 4 weeks in HDSS in subjects randomized to treatment (p_T) will be lower than or equal to that in subjects randomized to sham (p_S), $p_T \leq p_S$

H_a: The proportion of subjects with improvement of at least 2 grades from baseline to 4 weeks in HDSS in subjects randomized to treatment (p_T) will be greater than that in subjects randomized to sham (p_S), $p_T > p_S$

Success is defined as a statistically significant difference (at the 0.05 two-sided significance level) between proportions of patients with at least 2 grade improvement in HDSS from baseline to 4 weeks between randomized group using CMH test stratified by baseline HDSS (3 vs. 4).

4. **Proportion of subjects with at least 50% improvement in gravimetric sweat production (GSP) in subjects treated with the N-SWEAT Patch only at 4-weeks. (GSP will be calculated based on the total sweat produced by both axillae.)**

H_o: The proportion of subjects with at least 50% improvement in gravimetric sweat production (GSP) in subjects randomized to treatment (p_T) is not statistically significantly different from 0, $p_T = 0$.

H_a: The proportion of subjects with at least 50% improvement in gravimetric sweat production (GSP) in subjects randomized to treatment (p_T) is statistically significantly different from 0, $p_T \neq 0$. Success is defined as a statistically significant result (at the 0.05 two-sided significance level). It is expected that at least 50% of subjects will have at least 50% improvement in gravimetric sweat production from baseline at 4-weeks.

9.10.2.3 Secondary Objectives

9.10.2.3.1 To compare the mean improvement over baseline for QOL scale Bother between subjects randomized to treatment as compared to sham

Subjects Included in Analysis: All FAS subjects will be included in the analysis.

Endpoint(s): QOL scale Bother score

Statistical Analysis: An analysis will be performed using all available time points with complete follow-up at the time of the analysis. A generalized linear mixed model be used to compare average change in QOL Bother from baseline to follow-up between randomized groups over time on study. The dependent variable change in QOL Bother from baseline to follow-up with independent variables to include randomized group, follow-up time, baseline HDSS and two-way interaction terms. The covariance structure among the compound symmetric, auto-regressive and unstructured that provides the best model fit by the Schwarz BIC criterion will be chosen.

A hierarchical stepwise backward elimination technique will be used to reduce the model. The two-way interactions will be reviewed first, the two-way interaction with the largest p-value provided that p-value is greater than 0.05 will be removed from the model and the model refit and repeated until only two-way interactions with p-values < 0.05 are retained. The main effects for any two-way interaction retained in the model must remain in the model as well as the randomized treatment. That being said, the main effects will be evaluated in the same manner as the two-way interaction terms. This analysis will be repeated in the PP population.

9.10.2.3.2 To compare the mean improvement over baseline for QOL scale Impact between subjects randomized to treatment as compared to sham

Subjects Included in Analysis: All FAS subjects will be included in the analysis.

Endpoint(s): QOL scale Impact score

Statistical Analysis: An analysis may also be performed using all available time points with complete follow-up at the time of the analysis. A generalized linear mixed model be used to compare average change in QOL Impact from baseline to follow-up between randomized groups over time on study. The dependent variable change in QOL Impact from baseline to follow-up with independent variables to include randomized group, follow-up time, baseline HDSS and two-way interaction terms. The covariance structure among the compound symmetric, auto-regressive and unstructured that provides the best model fit by the Schwarz BIC criterion will be chosen.

A hierarchical stepwise backward elimination technique will be used to reduce the model. The two-way interactions will be reviewed first, the two-way interaction with the largest p-value provided that p-value is greater than 0.05 will be removed from the model and the model refit and repeated until only two-way interactions with p-values < 0.05 are retained. The main effects for any two-way interaction retained in the model must remain in the model as well as the randomized treatment. That being said, the

main effects will be evaluated in the same manner. This analysis will be completed in the PP population as well.

9.10.2.3.3 To compare the proportion of patients with at least a 2 grade improvement in HDSS from baseline between subjects randomized to treatment as compared to sham

Subjects Included in Analysis: All FAS subjects will be included in the analysis.

Endpoint(s): HDSS.

Statistical Analysis: The proportion of patients with at least a 2 grade improvement in HDSS from baseline to 4 weeks will be compared between treatment vs. sham using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HDSS value of 3 vs. 4 in the FAS population. Statistical significance is achieved with two-sided p-value <0.05 equivalent to one-sided p-value < 0.025. This analysis will be completed in the PP group as well.

An analysis will be performed using all available time points with complete follow-up at the time of the analysis. A generalized linear mixed model will be used to compare the proportion of subjects with at least 2 grade improvement from baseline to 4 weeks between randomized groups over time on study. The dependent variable is 2 grade improvement over baseline (Y/N) with independent variables to include randomized group, follow-up time, baseline HDSS and two-way interaction terms. The covariance structure among the compound symmetric, auto-regressive and unstructured that provides the best model fit by the Schwarz BIC criterion will be chosen.

A hierarchical stepwise backward elimination technique will be used to reduce the model. The two-way interactions will be reviewed first, the two-way interaction with the largest p-value provided that p-value is greater than 0.05 will be removed from the model and the model refit and repeated until only two-way interactions with p-values < 0.05 are retained. The main effects for any two-way interaction retained in the model must remain in the model as well as the randomized treatment. That being said, the main effects will be evaluated in the same manner as the two-way interactions. This analysis will be completed in the PP group as well.

9.10.2.3.4 To estimate the proportion of subjects randomized to treatment with at least 50% improvement from baseline to 4 weeks in gravimetric sweat production (GSP)

Subjects Included in Analysis: All FAS subjects randomized to receive the N-SWEAT patch.

Endpoint(s): The average of 2 accurate GSP measurements will be conducted for each Axilla at each time point. The total sweat production at each timepoint will be calculated by summing the average sweat production from both axilla. The percentage change at 4 weeks will be calculated based on the total sweat production at baseline and 4 weeks.

Statistical Analysis: The potential confounding factors of room temperature, position during evaluation and time of evaluation will be summarized for baseline and 4 weeks. The difference in temperature, time of evaluation and whether or not the baseline and 4 week evaluation were performed in the same or different position will be summarized. These factors will be evaluated with respect to their relationship with the endpoint and association with outlying values, if any, using graphical techniques and summary statistics. Depending on this evaluation, outlying values may be excluded from the analysis with justification provided and relationships, if any found, will be summarized.

The proportion of patients with 50% or greater improvement in percentage change from baseline to 4 weeks will be statistically compared to zero by calculating the Wilson's 95% two-sided confidence interval and comparing the lower bound to zero. If the lower bound is greater than zero, there is statistically significant evidence that the proportion of subjects with a clinically relevant improvement exists and is greater than 0. This analysis will be completed in the PP population as well.

9.10.3 Observational Endpoints

Observational endpoints will be summarized at all available time points at the time of analysis. These endpoints will be analyzed with standard statistical methods summarized in detail in the stand-alone statistical analysis plan that will be completed prior to formal analysis of the data. Standard statistical methods will be employed consistent with those summarized for the secondary endpoints. Statistical significance will be determined based on a two-sided p-value of 0.05. Only summary statistics (no p-values or 95% confidence intervals) will be provided in labelling upon agreement between Candesant and FDA. The p-values for the observational endpoints will not be adjusted for multiplicity and should be interpreted with caution.

- Baseline-adjusted mean improvement in QoL-7 instrument assessed by treatment group.
- Composite - proportion of patients with HDSS 1 or 2 AND 50% improvement in GSP assessed by treatment group.
- Composite - proportion of patients with HDSS 1 or 2 AND 75% improvement in GSP assessed by treatment group.
- Duration of efficacy: time from treatment to first observed reversion to HDSS 3 or 4 (a Kaplan-Meier analysis using median duration of efficacy will be compared between the treatment groups). Also performed for first reversion to subject's baseline HDSS.
- Mean change from baseline at 4 weeks in GSP by treatment group.

9.11 Specification of Subgroups for Analysis

The primary efficacy endpoint will be summarized within subgroups defined by Baseline HDSS, age, gender and race/ethnicity. Adverse events and local skin reactions will be summarized by Fitzpatrick Skin Types. It is important to note that the study is not powered to demonstrate statistical significance within subgroups and therefore it is not an expectation of the analysis that statistical significance be demonstrated with the subgroups.

10. ADVERSE EVENTS

10.1 Definitions

The definitions below are in accordance with ISO 14155. Both the investigator and the sponsor will comply with all local medical device reporting requirements.

Adverse Events (AEs) may occur during the investigational procedure or during the follow-up phase. AEs occurring prior to the use of the N-SWEAT device will be documented in the subject's medical record but will not count as related to the investigational device or procedure.

10.1.1 Adverse Events

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

10.1.2 Adverse Device Events

An Adverse Device Event (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.1.2.1 Treatment-Related Adverse Event

A treatment-related AE is any AE that starts on or after the time of treatment that a physician considers a result of treatment; the AE may or may not be related to the study device. Treatment-related events will be assessed for relationship to the device. The occurrence of treatment-related AEs will be summarized as part of the assessment for safety.

10.1.3 Serious Adverse Events

A Serious Adverse Event (SAE) is an AE that:

- Led to death.
- Led to serious deterioration in the health of the participant, that either resulted in:
  - A life-threatening illness or injury. The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
  - A permanent impairment of a body structure or a body function

- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

10.1.4 Serious Adverse Device Events

A Serious Adverse Device Event (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.

10.1.5 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.1.6 Unanticipated Adverse Device Events

According to 21 CFR 812.3(s), a Unanticipated Adverse Device Event (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.2 Adverse Event Review by Investigator

Each AE will be assessed by the investigator as to its relationship and level of relatedness to the device and/or procedure. In addition, the investigator will identify the date of onset, any required treatment or intervention, severity, and duration. All AEs will be monitored until they are adequately resolved, stabilized and/or explained.

10.2.1 Severity

The investigator will use the terms below to rate the severity of each AE.
Note that an event is defined as serious when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe per the table below.

Table 6. AE Severity

Severity	Description
Mild	Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
Moderate	Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning
Severe*	Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

Based on the National Institute on Aging (NIA) Adverse Event and Serious Adverse Event Guidelines (2018)
**Severe does not indicate an SAE (Serious Adverse Event). Please see 10.1.3 for a definition of Serious Adverse Event.*

10.2.2 Relationship to N-SWEAT Patch

The investigator will use the terms below to rate the relationship of the AE to the patch.

Table 7. AE Relationship to Device

Relationship	Description
Not Related	• not associated with patch • due to an underlying or concurrent illness or effect of another device or drug
Unlikely	• little or no temporal relationship to the patch • a more likely alternative etiology exists
Possible	• temporal sequence between patch 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 patch application completion/removal or • event cannot be reasonably explained by the Subject's condition
Highly Probable	• temporal sequence is relevant and • event abates upon patch application completion/removal or reappearance of the event on repeat patch application

10.3 Adverse Event Reporting

All AEs and ADEs will be recorded by the investigator or designee on the case report forms (CRFs) provided. The investigator at each site is ultimately responsible for reporting AEs to the IRB according to IRB requirements and to the sponsor in accordance with the Investigational Plan and applicable FDA regulations. The site will be instructed to report all AEs considered moderate or severe and all local skin reactions to Candesant within 5 working days of the identification of the AE.

If an Adverse Event is considered a local skin reaction within the treated area, photos are required to be submitted as part of the Adverse Event Report. Submitted photos should show documentation of AE onset, AE progression and/or healing and AE

resolution (if applicable). Photos are to be taken with a high-resolution camera with the arm in the standardized treatment position and adequately illuminated. Photos are to be marked with Subject ID, date and subject side (i.e. Right or Left). Photos are to be taken with a measurement calibration reference visible.

AEs or complications meeting the definition for UADEs must be reported by the investigator to the sponsor as soon as possible, but in no event, later than 10 working days after the investigator first learns of the event. The sponsor will conduct an evaluation of any reported UADEs and will report the results of this evaluation to the FDA, IRBs, and participating investigators within 10 working days after first receiving notice of the event.

Descriptive and photographic data will be recorded and maintained on file for all AEs regardless of severity or device-relatedness. All observed local skin reactions will also be recorded.

10.4 Independent Adverse Event Review

An independent Data Safety Monitoring Board (DSMB) will be established to protect patient safety and ensure data integrity for the Sahara Study. The board will be comprised of 3-5 clinical physicians with expertise in dermatology who are not participants in the study. The DSMB will serve in three roles in the safety overview of the Sahara study:

- To convene as needed for review of Adverse Events related to stopping rules and to determine a root cause analysis of these events.
- To conduct a monthly blinded review of all AEs reported during enrollment and until the final subject has reported for 4-week follow-up.
- If warranted, to request unblinding and fully investigate any potential safety signal. This investigation may result in a recommendation to stop the clinical study if the findings indicate an unacceptable or unknown safety risk.

A charter will establish the DSMB details on the operation of the DSMB.

11. RISK-BENEFIT ASSESSMENT

11.1 Potential Benefits

It is expected that the Candesant Biomedical N-SWEAT Patch may provide some benefit to the subject by reducing the amount of sweat that they produce after treatment. This sweat reduction would be expected to offer a quality of life improvement to the subject. The true benefits are not fully known but will be assessed and measured during this study. It is possible that there is no benefit to the N-SWEAT Patch.

Since this a randomized study with a sham control, the subjects who receive the sham patch are not expected to have any immediate benefit in the reduction of sweating with their participation. However, their participation may be beneficial in the future in helping to assess the potential of having this technology available to all patients with excessive sweating or primary hyperhidrosis.

11.2 Potential Risks

The identified potential risks to the study subject that may be associated with treatment for excessive sweating or hyperhidrosis of the axilla are shown below. The risks of these events occurring for subjects treated during the Sahara Study have been mitigated as much as possible by device design and training

- Allergic reaction to device materials
- Blister formation
- Burning or stinging
- Decreased hair growth
- Discomfort / Pain
- Discomfort during post-treatment cleaning
- Infection
- Injury to eyes or mouth, if gloves or hands that handled the device touch
- Intolerance of deodorant
- Irritation
- Itching, tightness, tingling
- Numbness or altered sensation
- Redness (erythema), blotchiness, bumps
- Scar or contracture
- Skin corrosion
- Skin discoloration
- Skin erosion
- Sweating in other parts of the body
- Swelling (edema) or bruising
- Thermal Injury

11.3 Minimization of Anticipated Risks

Risks associated with the N-SWEAT Patch are minimized by design and training. Risks are minimized under this protocol due to:

- Only operators with proper training and experience will use the device
- Clinician users will be given the opportunity to use their discretion and medical expertise throughout the treatment and appropriately respond to the patient's reaction to treatment
- Only certified personnel will dispose of the device
- Extensive non-clinical evaluation of the device (animal and bench top testing)
- The use of standard medical grade materials in the manufacture of the device

11.4 Protocol Compliance

As with any clinical investigation, it is critical to conduct the study per the study protocol so as to not compromise the study results. Areas of particular criticality are as follows:

- Eligibility criteria (all treated subjects must be eligible per the protocol)
- Compliance with the protocol follow-up activity including patient reported outcomes and quality of life assessments
- Thorough, accurate, and timely reporting of AEs
- Thorough, accurate, and timely reporting of all clinical trial data

11.5 Safety-Related Stopping Rules

The study sponsor will be charged with monitoring the study for safety and for auditing the quality of the data. Stopping rules will be activated if there are any perceived safety concerns related to the N-SWEAT Patch as demonstrated by the occurrence of any of the following:

FIRST 10 SUBJECTS

1. One report of a Serious Adverse Event due to:
   - thermal or caustic injury
   - blister
   - erosion
   - pustule
   - erythema lasting > 7 days or developing >7 days after the treatment
   - infection
   - suspected infection of the skin or soft tissue in the axilla

AFTER 10 SUBJECTS

1. If 10% of N-SWEAT treated subjects have a reported severe device-related Adverse Event as defined in Table 6, or

2. If the DSMB recommends stopping due to a safety signal as described in section 10.4.

Should a stopping rule be triggered:

1. Enrollment and treatment will be suspended and a root cause investigation into all involved AEs will be conducted within 5 days by an independent Data Safety Monitoring Board to determine the cause of the event(s), to look at any trends and to evaluate potential safety issues.

2. A full report (including photos, description, onset, duration, severity, causality, intervention, and sequalae) will be sent to FDA no later than 5 working days after DSMB review is complete.

3. Candesant will work with FDA, DSMB and study investigators to establish a process to re-start the study.

12. STUDY MANAGEMENT

For this study, Candesant Biomedical will have certain direct responsibilities and will delegate other responsibilities to appropriate consultants and Clinical Research Organizations (CROs). Together, Candesant, consultants, and CROs will ensure that the study is conducted according to the protocol and all applicable regulations.

12.1 Key Study Contributors

A Master Contact List will be maintained to include all key study personnel (e.g., monitors, data management personnel) and reviewing IRBs as well as the primary site contacts (investigators, study coordinators). The Master Contact List will be provided to the study sites.

All personnel to participate in the conduct of this clinical study will be qualified by education or experience to perform their tasks.

12.2 Regulatory Considerations

As the study sponsor, Candesant Biomedical has the overall responsibility for the conduct of the study in accordance with 21 CFR 812; E6 Good Clinical Practice (GCP) Consolidated Guidance; and any conditions imposed by FDA or the reviewing IRB(s). The study will not commence until the necessary approvals have been obtained. The rights, safety and well-being of clinical investigation subjects have been protected in a manner consistent with the ethical principles that have their origin in the Declaration of Helsinki, as amended.

12.3 Approved Informed Consent

The sponsor will provide each study center with an example Informed Consent Form (ICF). The study center, to meet specific requirements, may modify this example ICF; however, the ICF to be used for subject consent under this protocol must contain all of the elements required by the study sponsor. The sponsor and the investigational site shall develop a mutually agreed upon ICF. The reviewing IRB must review and approve the ICF prior to use. The original signed and dated ICF for each subject must be retained by the investigational site for monitoring, and a copy provided to the Subject.

12.4 IRB Approval

IRB approval is required prior to study commencement. IRB approval is also required for any protocol amendments. The investigator is responsible for fulfilling any conditions of approval imposed by the reviewing IRB. IRB renewal should be obtained as required. Documentation of all IRB approvals and renewals will be maintained in the study files.

12.5 Amendment to the Study Protocol

The sponsor is responsible for management, processing, and approval of any amendment to the study protocol. Study protocol amendments will be submitted to FDA, to the reviewing IRB(s) and to other governing agencies, as applicable. Any necessary approvals will be received in writing before the requested change is implemented.

12.6 Protocol Deviation

Measures will be taken to ensure compliance with the study protocol. Investigators may request approval from Candesant Biomedical and, where applicable, from the reviewing IRB, if they identify a situation in which a deviation from the protocol is warranted. Prior approval is not necessary when the deviation is intended to protect the life or physical well-being of a subject in an emergency. Protocol deviation waivers, when issued, shall be documented in writing and maintained in the study files. Prior approval is not expected in situations where unforeseen circumstances are beyond the investigator's control, (e.g., subject was not available for scheduled evaluation); however, such event is still considered a deviation and will be reported on the appropriate CRF.

Deviations must be reported to Candesant Biomedical regardless of whether medically justifiable, pre-approved by the sponsor, or taken to protect the subject in an emergency. Subject related deviations will be reported on the Protocol Deviation CRF. Non-Subject-specific deviations (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a clinician who has not signed an investigator agreement or not been trained in the use of the patch) will be reported to the sponsor. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

Regulations require that investigators maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol.

12.7 Investigational Device Accountability

12.7.1 Device Records

The sponsor will only distribute investigational devices to sites that are part of the clinical investigation. The sponsor will maintain complete, current and accurate records pertaining to the distribution of the investigational devices and follow record keeping requirements in accordance with GCP and FDA Regulations.

The investigator is responsible for maintenance of adequate records of the receipt, disposition, and/or return of all investigational devices distributed to their site.

12.7.2 Device Use

The device must be used in accordance with the study protocol and the instructions for use provided with the device. Prior to use, investigators should inspect the product package and product label. Irregularities in packaging or labeling concerns should be notified to the sponsor immediately. Product demonstrating any potential packing integrity issue or expired product must not be used.

Access to the device inventory at the study site will be controlled and housed in a secure location. Use of the investigational device outside of the protocol is strictly forbidden and may constitute grounds for removal of the investigator/site from the study. After use the N-SWEAT Patch must be disposed of per the IFU instructions and in consideration of the facility's standard institutional practice.

12.7.3 Device Return

At study termination, the sponsor will provide specific instructions to the study sites on unused investigational devices.

If the device is associated with a possible device-related AE or device deficiency, the device should be returned to Candesant Biomedical for evaluation per instructions from the sponsor.

12.8 Training

12.8.1 Site Training

All investigators/trial personnel are required to attend sponsor training sessions, which may be conducted at an investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone training will take place as required. Training of investigators/study personnel will include, but is not limited to, the investigational plan, investigational device usage, protocol requirements, case report form completion, and trial personnel responsibilities. All investigators/study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Investigator/trial personnel must not perform any study-related procedures prior to being trained.

12.8.2 Monitor Training

The sponsor or designee will engage monitors that are qualified by appropriate training and experience to review the conduct and quality of the study. Prior to working on the study, monitors will be trained to the investigational plan, case report forms, and device specifications. Such training will be documented.

12.9 Monitoring

Monitors engaged by the sponsor and/or designee will monitor the study over its duration according to standard operating procedures and the pre-specified monitoring plan. The study monitor will visit each site at appropriate intervals to review

investigational data for accuracy and completeness and ensure compliance with the protocol, FDA regulations, and IRB requirements. The study monitor may inspect all study related documents and required records that are maintained by the investigator/site.

The investigator/site will permit access to such documents including medical records (office, clinic or hospital) for the patients in this study. Source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, IRB submissions/approvals, and device information. Furthermore, the investigator and/or research coordinator will be available for monitoring visits. It is also expected that the investigator will provide the study monitor with a suitable working environment for review.

12.10 Ethical Considerations

The rights, safety, and well-being of subjects shall be protected consistent with the ethical principles that have their origin in the Declaration of Helsinki. These principles shall prevail over interests of science and society and shall be understood, observed, and applied at every step in this clinical study.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The sponsor and the investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

12.11 Protection of Subject Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data shall be secured against unauthorized access. Privacy and confidentiality of information about each subject shall be preserved in the reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All CRFs or other study-related data (such as imaging) will be tracked, evaluated, and stored using only this unique identifier.

The investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The investigator bears responsibility for keeping this list confidential. A copy of this list will not be provided to the study sponsor and is only to be used at the study center.

While on site, monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the CRF corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include but is not limited to the subject's name, address, date of birth, gender, race, and medical record number. The subject's name, medical record number, or address will NOT be recorded in the monitor's visit report or the database.

Any source documents copied for monitoring purposes by the sponsor will be identified by using the assigned subject's unique identifier in an effort to protect subject confidentiality. Any subject identifiers will be blacked or scratched out and replaced with the subject's study identification code.

Photographs of the procedure and treatment areas will not include subject faces or any other personally identifying features. Subject images will be tracked using the unique study ID.

12.12 Quality Assurance and Supervision by Authorities

All documents and data shall be produced and maintained in such a way to assure control of documents and data to protect the subject's privacy as far as reasonably practicable. The sponsor and representatives of the FDA or other regulatory authorities are permitted to inspect the study documents (e.g., study protocol, CRFs, and original study-relevant medical records/files) as needed. All attempts will be made to preserve subject confidentiality.

All clinical sites are subject to audit by sponsor or designee for protocol adherence, accuracy of CRFs, and compliance with applicable regulations. Any evident pattern of non-compliance with respect to these standards will be cause for corrective action.

The study protocol, data-recording procedures, data handling, and study reports are subject to an independent clinical Quality Assurance audit by the study sponsor, its designee, or health authorities.

12.13 Corrective and Preventative Action

Aside from an official site audit, non-compliance may be discovered through other means such as monitoring, site management, general communication, or site visits. Any evident pattern of non-compliance with respect to 21 CFR 812, E6 GCP Consolidated Guidance, the Declaration of Helsinki, or conditions imposed by the reviewing IRB(s), the study protocol, or other governing requirements may be cause for corrective action. Such corrective action may range from communication of the non-compliance to the site being placed on probation until corrective action is taken. In more serious circumstances, enrollment may be terminated at the site. Corrective actions will be followed through resolution, and any resulting documentation surrounding the corrective and preventative action will be kept in the central study files.

12.14 Insurance

The sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

13. RESPONSIBILITIES

13.1 Sponsor Responsibilities

Candesant Biomedical, Inc. is the sponsor of this study. The study sponsor has the overall responsibility of the study and will work to ensure compliance with the study protocol, 21 CFR 812, GCP: Consolidated Guidance, and signed study agreements. The sponsor will be responsible for, but not limited to, the following:

- Select qualified investigators, monitors, and contract study personnel
- Maintain Control and properly manage all Investigational Devices
- Obtain required agreements including investigator eligibility and financial disclosure
- Provide the study protocol and any subsequent amendments to the investigators
- Provide appropriate information and training to investigators and study site staff
- Ensure that no study related activities commence at any site prior to receipt of all required documented approvals, at minimum FDA and IRB
- Promptly inform the investigators and where applicable any regulatory authorities and IRBs if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Provide protocol-initiation training to include review of the IFU, CRF completion, and guidelines for obtaining informed consent
  - Each study center will undergo Site Initiation which will include but is not limited to a review of the following by key study personnel (investigators, coordinators):
    - Study Protocol
    - Consenting procedures
    - IFU
    - AE Reporting requirements
    - CRF completion
    - Device handling and accountability procedures
    - Protection of subject confidentiality
- Coordinate ongoing communication with CRO(s), consultants, and study sites to resolve any problems concerning the protocol or data collection. Every effort will be made to ensure compliance with the protocol
- Retain ownership of all clinical data generated in this study and control the use of the data for purposes of regulatory submissions
- Protect subject confidentiality
- Collect, store, and keep secure, at a minimum, the following documents:
  - Curriculum Vitae (CV) of each investigator
  - The name of the institutions where the study will be conducted
  - The IRB opinion and/or approval, in writing, and relevant correspondence
  - IRB-approved ICF
  - Correspondence with authorities (as required)
  - Investigator Agreement for each investigator
  - Conflict of Interest and Financial Disclosure Form for each investigator
  - Protocol Signature Page

- Insurance certificates (as necessary)
- Names/contact information for study monitor(s)
- Records of any AEs
- Statistical analyses and underlying supporting data
- Final report

13.2 Sponsor Maintenance of Study Records

The sponsor will be responsible for maintaining study records per 21 CFR 812.140(b) and GCP: Consolidated Guidance.

The sponsor will be responsible for monitoring the investigation per 21 CFR 812.46 and GCP: Consolidated Guidance.

The sponsor will be responsible for reporting per 21 CFR 812.50(b).

13.3 Investigator Responsibilities

The investigator(s) shall be responsible for the day-to-day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation. The investigator is expected to be compliant with the Study Protocol, Investigator Agreement, Instructions for Use and other provided materials at all times.

To ensure proper execution of the study protocol, each investigator can identify a study coordinator for this study. Working with and under the authority of the investigator, the study coordinator can help assure that all study requirements are fulfilled and is the contact person at the site for all aspects of study administration. The investigator is responsible for ensuring that the study coordinator and all other study staff at the clinical site are compliant with the study requirements.

The investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The study center will also maintain original source documents from which study-related data are derived, which may include, but are not limited to:

- Progress notes recording subject's medical history and medications
- Medical records regarding AEs, including treatment and clinical outcome
- Notes of phone calls and/or correspondence concerning the subject

The investigator must ensure that all study subject records are stored for at least 2 years after the date a marketing application is approved for the device for the indication for which it is being investigated or, if no application is to be filed, until 2 years after the applicable agency(ies) has been notified (if applicable). To avoid error, the study site must contact Candesant Biomedical prior to the destruction of study records to ensure that they no longer need to be retained. In addition, Candesant Biomedical is to be contacted if the investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

The investigator(s) will allow auditing of their clinical investigation procedure(s).

13.4 Investigator Reports

The investigator(s) will be responsible for reporting per 21 CFR 812.150(a) and according to applicable IRB requirements and GCP: Consolidated Guidance. Reports must identify subjects using the unique identifier to protect confidentiality.

13.5 Required Documents from the Investigator

At a minimum, the following documents will be provided by the investigational site to the study sponsor prior to study start (consent of the first subject):

- Signed Investigator Agreement
- Documentation of Financial Disclosure
- Signed Protocol Signature Page
- IRB approval
- IRB approved ICF
- Investigator and Co-investigator's current CV

A site may not begin study participation until all of the above-listed documents have been provided to the study sponsor. The study may begin once the CV of the site Principal Investigator has been received. No additional investigators may participate until a copy of their CV and a signed Investigator Agreement has been provided to the study sponsor.

Additional study-required documents will be collected, as applicable, and maintained, as necessary.

13.6 Other Investigator Reports

The investigator for each study center is responsible for submission of reports to the sponsor according to the schedule shown below. All reporting timelines are "within knowledge of the occurrence." Reports must identify subjects using the study's unique identifier to protect subject's confidentiality.

Type of Notification	Time Constraints
Withdrawal of IRB Approval	verbal report within 24 hours followed by a written report within 5 working days
Informed Consent NOT Obtained	verbal or written report within 5 working days

14. DATA MANAGEMENT

Study data will be collected using a standardized eCRF. The CRF will be designed to accommodate the specific features of the study design. Modification of the CRF will only be made if deemed necessary to support the study design and will be done by the study sponsor.

14.1 Data Management Responsibilities

Candesant Biomedical will be responsible for the management of the database and resulting study data. Conventional data verification routines will be performed. Data Management will be performed according to the study's Data Management Plan. The study sponsor may manage directly or outsource data management to a qualified data management group.

14.2 Data Entry

Subject data will be recorded on CRFs and entered into a limited access secure database. The software and database will be compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures.

Changes made to the clinical data will be captured in an audit trail and available for review.

14.3 Data Cleaning

Data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created and the resulting Data Clarification Form, or equivalent, issued to the clinical site(s) for appropriate resolution (as applicable).

14.4 Data Retention and Back-up

System backups are performed regularly. The database will be managed on a secure server and computer access password controlled. The secure server will be backed up periodically. Upon study completion, the data will be archived.

14.5 Confidentiality and Security

Passwords will be utilized by data entry, data verification, and other personnel who have database access to ensure confidentiality and protection of data.

15. STUDY CLOSE-OUT

At the time of the site close-out visit, the site monitor or designee will collect all outstanding study documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented in a close-out visit report.

Once all sites are considered closed, the study may be closed. Study closeout will include a final report which will be submitted to each participating investigator, IRB, and other governing agency, as required.

15.1 Study Suspension or Early Termination

The study can be discontinued at the discretion of the investigator or study sponsor for reasons including, but not limited to, the following:

- Occurrence of AEs unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known AEs
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- UADE presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB or regulatory requirements

If the study is discontinued or suspended prematurely, the sponsor shall promptly inform all clinical investigator(s)/investigational center(s) of the termination or suspension and the reason(s) for this. The IRB shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the clinical investigator/investigational center(s). Regulatory authorities and the personal clinician(s) of the subjects may also need to be informed if deemed necessary.

15.2 Final Report

A final report will be prepared even if the study is prematurely terminated.

15.3 Publication Policy

At the conclusion of the study, a multi-center abstract reporting the results will be prepared and may be presented at a major meeting(s). A multi-center publication may also be prepared for publication in a reputable scientific journal. The publication of results from any single center experience within the study is not allowed until the aggregate study results have been published, unless there is written consent from the study sponsor.

16. ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Event
CDX-101	N-SWEAT Patch was previously called CDX-101
CLP	Clinical Protocol
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Clinical Research Organization
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FACES	Wong-Baker Pain Scale
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GEE	General Estimating Equation
GSP	Gravimetric Sweat Production
HDSS	Hyperhidrosis Severity Scale
ICF	Informed Consent Form
ICH	International Council on Harmonization
ID	Identifier
IDE	Investigation Device Exemption
IFU	Instructions for Use
IHHS	International Hyperhidrosis Society
IRB	Institutional Review Board
ITT	Intent to Treat
N-SWEAT	Candesant Biomedical Patch to reduce sweating
PPS	Per Protocol Set
QoL	Quality of Life
QoL-7	A Specific QoL Survey with 7 questions
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STAYDRI	**S**afe**T**y and Feasibilit**Y** Evaluation of the CDX-101 **D**evice in Patients who Expe**Ri**ence Heavy or Excessive SweatIng
UADE	Unanticipated Adverse Device Event
US	United States

17. References

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APPENDIX A: HDSS

Information and Instructions:

About Sweating:
Sweating is a natural and healthy part of life. Sweating helps to cool the body and maintain a normal body temperature in a warm environment or during exercise. It is normal to sweat when you are hot, when you are exercising, and when you are feeling stressed.
About Excessive Sweating:
You are in this study because you feel like you sweat too much. You may sweat at times other than when you are warm, exercising, or stressed. The questions below are designed to measure the severity and impact of your excessive underarm sweating during the past week. While you may experience excessive sweating on other parts of your body, these questions are designed to measure the impact of the treatment on your underarm sweating ONLY.
Instructions:
• **Please only think about your underarm sweat as you answer these questions.** • **Please remember that sweating when you are hot, exercising or stressed is normal, so when you are answering the questions, think about sweating that is beyond normal.** *For example, you may sweat when you work out at the gym and still answer "never" since sweating at the gym during a strenuous workout is considered to be the body's natural response to keep the body cool.* • There are no right or wrong answers; you should answer truthfully about your excessive underarm sweating experiences during this past week • If you have any questions, you may contact the study team

The box next to the statement that best describes your feelings about your underarm sweating at the current time should be checked.
Prior to each statement there is a number (1, 2, 3, and 4). This number is the "HDSS score".

HDSS SURVEY		
ASSESSMENT TIME: ☐ Screening ☐ Baseline ☐ 1 week ☐ 2 weeks ☐ 3 weeks ☐ 4 weeks ☐ 5 weeks ☐ 6 weeks ☐ 7 weeks ☐ 8 weeks ☐ 9 weeks ☐ 10 weeks ☐ 11 weeks ☐ 12 weeks ☐ Other	☐ **1.**	My underarm sweating is never noticeable and never interferes with my daily activities
	☐ **2.**	My underarm sweating is tolerable but sometimes interferes with my daily activities
	☐ **3.**	My underarm sweating is barely tolerable and frequently interferes with my daily activities
	☐ **4.**	My underarm sweating is intolerable and always interferes with my daily activities

APPENDIX B: LOCAL SKIN REACTIONS

An assessment for local skin reactions is conducted by the investigator pre-treatment, immediately post-treatment and at all clinic visits following treatment. . The assessment is also used during the course of evaluating and reporting an AE that is a local skin reaction.

The overall scoring system is comprised of an erythema rating scale plus the addition of clinical descriptors adapted from Dykes, 1992 and the FDA Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (1999). The severity of erythema is rated on a scale of 0–5 along with the presence of other clinical signs or symptoms. These descriptors noted by letters, are then added to the numerical score (e.g., 3S). *For example: Erythema spreading outside the treatment site with subject reporting scaling = 3 S*

Table 8: Skin Erythema Assessment

Rating	Description
0	No reaction/No erythema
1	Minimal erythema (barely perceptible)
2	Erythema (easily visible)
3	Erythema, spreading outside of treated site
4	Erythema, spreading outside of treated site with either edema (swelling) or vesicles (elevated, circumscribed lesions up to 1 cm in size that are filled with serous fluid)
5	Severe reaction with ulceration (irregularly sized and shaped erosions of the skin extending into the dermis)

Table 9: Clinical Signs/Symptom Descriptors*

Descriptor	Description
□ O	No Clinical Signs/Symptoms
□ BS	Burning or stinging (sensation as described by the subject)
□ I	Itching (sensation as described by the subject)
□ E	Edema
□ S	Scaling
□ F	Fissures
□ C	Crusts
If C:	*Give Color: _____* *Thickness: □thin □thick* *Describe: □dry □macerated □adherent □loose* *Culture Results: □positive □negative □N/A*
□ V	Vesicles
If V:	*Give size _____ mm x _____mm*
□ BU	Bulla
If BU:	*Give size _____ mm x _____mm*
□ P	Pustule
If P:	*Give size _____ mm x _____mm*
□ R	Erosion
If R:	*Give size _____ mm x _____mm*
□ U	Ulcer
□ A	Scarring
If A:	*☐ Contracture ☐ Hypertrophic ☐ Keloid*
□ OTH	Other
If OTH:	*Describe Other:*

*Clinical Symptoms are assessed as mild, moderate or severe per **Table 6** of this protocol.

APPENDIX C: QoL SURVEYS

Information and Instructions for Study Subjects:

About Sweating:
Sweating is a natural and healthy part of life. Sweating helps to cool the body and maintain a normal body temperature in a warm environment or during exercise. It is normal to sweat when you are hot, when you are exercising, and when you are feeling stressed.
About Excessive Sweating:
You are in this study because you feel like you sweat too much. You may sweat at times other than when you are warm, exercising, or stressed. The questions below are designed to measure the severity and impact of your excessive underarm sweating during the past week. While you may experience excessive sweating on other parts of your body, these questions are designed to measure the impact of the treatment on your underarm sweating ONLY.
Instructions:
• **Please only think about your underarm sweat as you answer these questions.** • **Please remember that sweating when you are hot, exercising or stressed is normal, so when you are answering the questions, think about sweating that is beyond normal.** *For example, you may sweat when you work out at the gym and still answer "never" since sweating at the gym during a strenuous workout is considered to be the body's natural response to keep the body cool.* • If you have any questions, you may contact the study team

QUALITY OF LIFE ASSESSMENT QUESTIONS		*Version: Draft _IDE Submission*	
TIME OF ASSESSMENT: ☐ Baseline ☐ 1 week ☐ 2 weeks ☐ 3 weeks ☐ 4 weeks ☐ 5 weeks ☐ 6 weeks ☐ 7 weeks ☐ 8 weeks ☐ 9 weeks ☐ 10 weeks ☐ 11 weeks ☐ 12 weeks ☐ Other	**BOTHER:** **During the past week how bothered were you by your underarm sweating?**	☐ Not at all bothered ☐ A little bothered ☐ Moderately bothered ☐ Very Bothered ☐ Extremely Bothered	
	IMPACT: **During the past week how often did your underarm sweating impact your daily activities?**	☐ Not at all ☐ A little bit ☐ A moderately amount ☐ A great deal ☐ An extreme amount	
	QoL-7: **How has your underarm sweating impacted certain areas of your life over the past week?** ***Please indicate Yes or No to the following statements***		
	1. I felt embarrassed because of my underarm sweating		☐Y ☐N
	2. I felt frustrated because of my underarm sweating		☐Y ☐N
	3. I felt less confident because of my underarm sweating		☐Y ☐N
	4. I had to change my shirt during the day because of my underarm sweating		☐Y ☐N
	5. I had to take more than 1 shower or bath a day because of my underarm sweating		☐Y ☐N
	6. My underarm sweating kept me from doing an activity that I wanted or needed to do		☐Y ☐N
	7. I wanted to avoid interactions with other people because of my underarm sweating		☐Y ☐N

APPENDIX D: GSP INSTRUCTIONS

Materials Required

- Quantitative Filter Papers, 90 mm
- Room temperature environment (26°C-30°C recommended). Actual room temperature must be documented to ensure that the same temperature is applied for each gravimetric test.

Procedure

GSP should be measured at screening, baseline (˜72 hours later) and at the 4-week follow-up visit. Measurements should be performed in the same position(s) (sitting, standing, or walking) at every visit. The position used should be document in the subject records. If the screening GSP Measurement and the Baseline GSP Measurement differ by more than 100%, the subject should not be enrolled. GSP should not exceed 300 mg/5 min in either axilla at either screening or baseline

IMPORTANT: Each gravimetric measurement must be taken in similar room conditions (same humidity and temperature as baseline). Whenever possible all Gravimetric tests for this study (screening, baseline and 4-weeks) should be taken at the same time of day (±3 hours).

A minimum of two (2) measurements should be taken in each axilla at every timepoint to ensure accuracy of results. If following the 2nd readings there is concern regarding the measurement accuracy, a 3rd reading may be performed. An average of accurate reading(s) will be reported.

- Weigh the plastic tube (vial) with filter paper to be used for the assessment (in milligrams) and document the baseline combined weight of the filter paper and vial.
- Dry the subject's axilla with an absorbent tissue or similar. Allow subject to sit for 15 minutes at room temperature (20-25.6°C)
- Determine the planned treatment area and desired location for filter paper placement. Paper should be placed centrally, just under the axilla crease formed when arms are down by their side.
- Place the previously weighed filter paper in the subject's armpit and ask them to hold it there for 5 minutes.

Following the 5-minute application of the filter paper, the filter paper and vial together will be weighed again. The result is the difference in the weight from baseline filter paper and vial weight and post filter paper application (paper placed in vial and weighed). The difference is calculated in milligrams and recorded as mg/5mins.

APPENDIX E: FITZPATRICK SKIN TYPE

The subject will be evaluated by the study site to determine their Fitzpatrick skin type based upon the categories as described below. The resulting skin type will be entered into the subjects CRF.

Skin Type I
Pale white skin, blue/green eyes, blond/red hair
Always burns, does not tan

Skin Type II
Fair skin, blue eyes
Burns easily, tans poorly

Skin Type III
Darker white skin
Tans after initial burn

Skin Type IV
Light brown skin
Burns minimally, tans easily

Skin Type V
Brown skin
Rarely burns, tans darkly easily

Skin Type VI
Dark brown or black skin
Never burns, always tans darkly

APPENDIX F: SAMPLE PATIENT DIARY

Daily Diary

Please remember to bring this diary to your 4-week follow-up appointment.

SAHARA STUDY

DAILY LOG: Week 1 **SUBJECT ID: ______________**

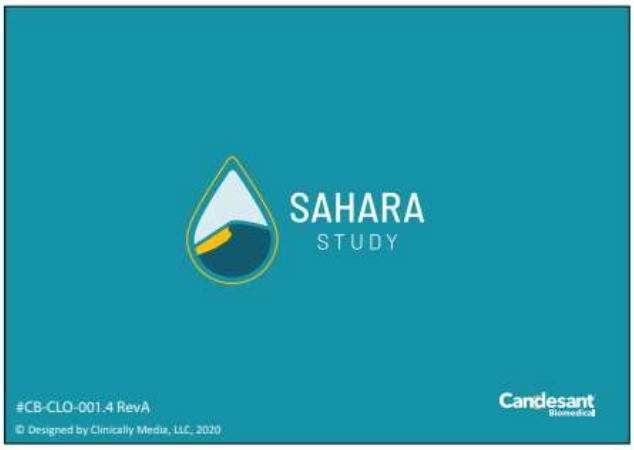
Day #	Date	PLEASE INDICATE ANY SYMPTOMS THAT YOU FEEL IN YOUR UNDERARMS
1		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*
2		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*
3		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*
4		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*
5		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*
6		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*
7		☐ None, I feel fine ☐ I have a continuing Symptom, OR ☐ I have a NEW Symptom – *Indicate Symptoms on the list below by Day #*

DETAILS:	Day 1	Day2	Day3	Day4	Day 5	Day 6	Day 7
Notes:	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________	☐ Pain ☐ Itch ☐ Redness ☐ Peeling skin ☐ Blister ☐ Infection (pus, discharge) ☐ Fever ☐ Other __________

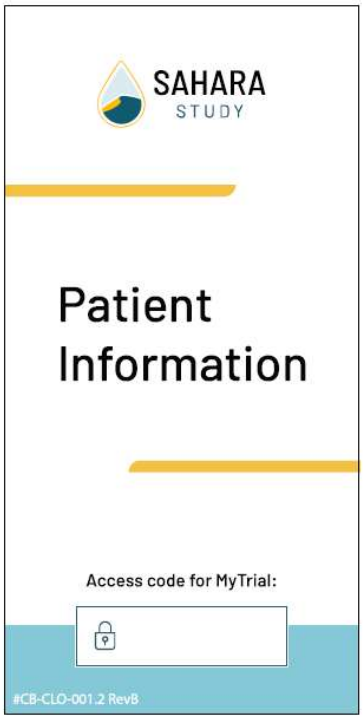
IF YOU EXPERIENCE ANY OF THESE SYMPTOMS, PLEASE CALL YOUR PHYSICAN RIGHT AWAY!!

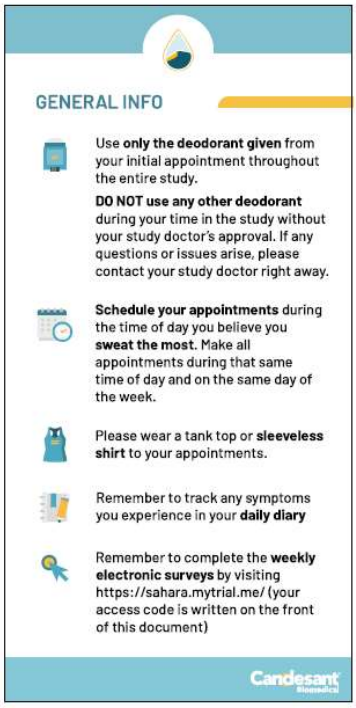
Appendix G: Sample Subject Take Home Care Hand-Outs

4. Post-Screening Postcard (CB-CLO-001.4, RevA)



2. Post-Treatment Hand-out (CB-CLO-001.2, Rev B)



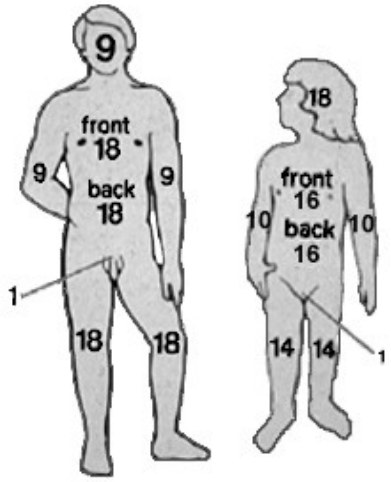


Appendix H: Referral to Burn Center*

Severity Determination

First Degree (Partial Thickness): Superficial, red, sometimes painful.
Second Degree (Partial Thickness): Skin may be red, blistered, swollen. Very painful.
Third Degree (Full Thickness): Whitish, charred or translucent, no pin prick sensation in burned area.

Percentage Total Body Surface Area (TBSA)



Burn Center Referral Criteria

A burn center may treat adults, children, or both. Burn injuries that should be referred to a burn center include:

1. Partial thickness burns greater than 10% total body surface area (TBSA).
2. Burns that involve the face, hands, feet, genitalia, perineum, or major joints.
3. Third degree burns in any age group.
4. Electrical burns, including lightning injury.
5. Chemical burns.
6. Inhalation injury.
7. Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality.
8. Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be initially stabilized in a trauma center before being transferred to a burn unit. Physician judgment will be necessary in such situations and should be in concert with the regional medical control plan and triage protocols.
9. Burned children in hospitals without qualified personnel or equipment for the care of children.
10. Burn injury in patients who will require special social, emotional, or rehabilitative intervention.

** Excerpted from Guidelines for the Operation of Burn Centers (pp. 79-86), Resources for Optimal Care of the Injured Patient 2006, Committee on Trauma, American College of Surgeons*

APPENDIX I: Sample Recruitment Poster/flyers (CB-CLO-001.1, Rev A)

APPENDIX J: DSMB QUALIFICATIONS

APPENDIX K: N-SWEAT IFU

Appendix L (for Participating Centers)