A PHASE 2, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED EFFICACY AND SAFETY STUDY OF GLYCOPYRRONIUM CLOTH, 2.4% IN PATIENTS WITH PALMAR HYPERHIDROSIS

Protocol Number	**DRM04-HH10**
Protocol Final Date	**11 December 2018**
Study Drug	**Glycopyrronium cloth, 2.4%**
IND Number	**104160**
Sponsor	**Dermira, Inc.** **275 Middlefield Road** **Suite 150** **Menlo Park, CA 94025** **USA**

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED EFFICACY AND SAFETY STUDY OF GLYCOPYRRONIUM CLOTH, 2.4% IN PATIENTS WITH PALMAR HYPERHIDROSIS

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SPONSOR SIGNATURE PAGE

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED EFFICACY AND SAFETY STUDY OF GLYCOPYRRONIUM CLOTH, 2.4% IN PATIENTS WITH PALMAR HYPERHIDROSIS

Protocol Number	**DRM04-HH10**
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The signature below constitutes approval of this protocol. I certify that I have the authority to approve this protocol on behalf of the Sponsor, Dermira, Inc. The study will be conducted in accordance with this protocol and all applicable laws, rules, and regulations and with the International Conference on Harmonisation Good Clinical Practice (ICH GCP), regulations of the United States (US) Food and Drug Administration (FDA), or according to the regulations of the country where the study is being conducted and the ethical principles that have their origin in the Declaration of Helsinki.

Authorized by:

Sponsor Signature

13 DEC 2018

Date (DD MMM YYYY)

Eugene A. Bauer, MD
Chief Medical Officer

INVESTIGATOR SIGNATURE PAGE

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED EFFICACY AND SAFETY STUDY OF GLYCOPYRRONIUM CLOTH, 2.4% IN PATIENTS WITH PALMAR HYPERHIDROSIS

I have read this protocol, including the appendices, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, according to the ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable laws, rules and regulatory requirement(s) including those of the United States (US) Food and Drug Administration (FDA) or according to the regulations of the country where the study is being conducted.

I agree to obtain the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol and informed consent prior to the start of the study.

I agree to obtain formal written informed consent in accordance with applicable federal and local regulations and international guidelines from all subjects prior to their entry into the study.

I have received and reviewed the Investigator's Brochure including the potential risks and side effects of the product and instructions for use.

I agree to report to the Sponsor any adverse events that occur during the course of the study in accordance with the ICH GCP guideline and the protocol.

I agree to ensure that all associates, colleagues, and employees assisting me with the conduct of the study are informed of their responsibilities in meeting the above commitments and the commitments set forth in the Investigator's Agreement.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with the ICH GCP guideline, and federal and local requirements.

I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

_____ _____

Investigator's Signature Date (DD MMM YYYY)

_____

Investigator's Name (print)

PROTOCOL SYNOPSIS

Title:	A phase 2, randomized, double-blind, vehicle-controlled efficacy and safety study of glycopyrronium cloth, 2.4% in patients with palmar hyperhidrosis
Protocol Number:	DRM04-HH10
Phase:	2
Number of Sites:	5-8 in the United States
Study Population:	Subjects ≥9 years of age with primary palmar hyperhidrosis
Sample Size:	Approximately 60
Study Treatment:	Glycopyrronium cloth, 2.4% applied to the hands once daily Vehicle cloth applied to the hands once daily
Randomization:	2:1 (active:vehicle)
Study Objective:	Assess the efficacy and safety of various application methods for glycopyrronium cloth, 2.4% when used to treat palmar hyperhidrosis
Duration of Subject Participation:	• Screening: maximum duration of 21 days • Treatment period: 14 days • Maximum total participation: approximately 35 days
Study Visit Schedule:	Screening, Baseline/Day 1, Day 4 (phone call), Weeks 1, 2 (End of Treatment/Exit)

Study Summary:

This study will assess glycopyrronium cloth, 2.4% in patients with primary palmar hyperhidrosis and compare the efficacy and safety of various application methods in order to determine an optimal method for use in palmar hyperhidrosis. The study is intended to assess four application methods (treatment groups) initially. Data from these cohorts will be reviewed and if needed, this protocol will be amended to add one or more treatment groups to assess additional application methods, with the objective of determining optimal conditions for use in palmar hyperhidrosis.

This study is randomized, double-blind, parallel group and vehicle controlled. All subjects will sign an informed consent and undergo screening for study eligibility. Key criteria for entry are diagnosed primary palmar hyperhidrosis for at least 6 months, a hand sweat severity score of ≥4 (NRS 0-10 pts) and a Hyperhidrosis Disease Severity Scale (HDSS) grade of ≥3 (HDSS grade 1-4). Approximately 60 eligible subjects, ≥9 years of age will be randomized to one of 4 treatment groups at the Baseline visit. Within each treatment group, subjects will be randomly assigned to receive active or vehicle in a 2:1 fashion, respectively. Treatment groups are based on residence time of the drug on the hands and outlined in Table 1.

Table 1: DRM04-HH10 Treatment Groups

Treatment Group		N (Active:Vehicle)
1	15 minutes with occlusion (non-latex glove)	10:5
2	30 minutes with occlusion (non-latex glove)	10:5
3	15 minutes	10:5
4	30 minutes	10:5

Subjects will be instructed on the application method and apply study drug at home once each day for 14 days. Subjects will return to the clinic for study visits at Week 1 and Week 2 and will be contacted by phone on Day 4 for safety. Subjects will exit the study at the Week 2 visit. Efficacy measures include a hand sweating severity score (11-pt numerical rating scale (NRS)), gravimetric measurement of hand sweat and the HDSS grade. Safety measures include adverse events, local skin reactions (LSRs), vital signs and physical exam, serum chemistry and hematology. Females of child-bearing potential will be tested for pregnancy.

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1 INTRODUCTION

1.1 Product Development Rationale

Hyperhidrosis is a condition of excessive sweating beyond what is physiologically required to maintain normal thermal regulation, and where the sudomotor system is functioning excessively for no apparent reason. The sudomotor system consists of neurons that control sweat output through activation of cholinergic receptors on sweat glands.

Primary hyperhidrosis (excessive sweating without a known cause) is localized (focal), is characteristically symmetric, and can affect the axillae, palms of the hands, soles of the feet, face, and other areas. Secondary hyperhidrosis can be either focal or generalized and results from any number of conditions, including endocrine, metabolic, neurologic, and cardiovascular disorders or can result from the use of medications.

In a survey of households in the United States, using the Hyperhidrosis Disease Severity Scale and items from the Hyperhidrosis Impact questionnaire, the prevalence of the disease was estimated to be about 4.8% [1].

In 2016 results from 1,985 survey participants showed that the most prevalent type of hyperhidrosis in the study sample was axillary (68%) followed by palmar (65%). Data published in 2016 found that the majority of primary palmar hyperhidrosis patients reported childhood onset and less than 12 years of age [2].

Hyperhidrosis can have a substantial and debilitating effect on quality of life. Several quality of life studies conducted on individuals with hyperhidrosis have shown that excessive sweating often impedes normal daily activities and can result in occupational, emotional, psychological, social, and physical impairment.[3, 4]

Current therapeutic options for treating hyperhidrosis vary by affected area and range from topical therapies to surgery. Nonsurgical treatments include topical application of aluminum chloride products (e.g., Drysol®), tap water iontophoresis with or without anticholinergics, oral dosing with anticholinergics (e.g., Robinul®), intradermal injection of botulinum toxin (Botox®), and application of microwave energy (e.g., miraDry®). Surgical techniques are reserved for patients with severe disease and include endoscopic transthoracic sympathectomy, excision of axillary sweat glands, and axillary liposuction. Limited efficacy and skin irritation limit the use of topical aluminum chloride products. Iontophoresis, though effective for some patients, is a time consuming and somewhat painful treatment. Oral anticholinergics are efficacious, but have substantial side effects (e.g., blurred vision, tachycardia, dry mouth, urinary retention, increased ocular tension, and constipation) that often outweigh benefits [5, 6]. Botulinum toxin injections are also effective; however, very few patients receive botulinum toxin due to the high cost and pain associated with the required multiple injections. miraDry, a microwave device designed to destroy sweat glands, appears to be effective, but is expensive, requires repeat treatment, and can be painful [7, 8]. Thus, there is a clear need for a safe, nonirritating, noninvasive, easy-to-use, and effective treatment for this indication.

Glycopyrrolate (glycopyrronium bromide) is a synthetic, quaternary ammonium compound with a well-known pharmacology (anticholinergic) that acts as a muscarinic receptor antagonist. As with other anticholinergic agents, glycopyrrolate inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves, such as sweat glands. Under physiologic conditions, glycopyrrolate dissociates generating the glycopyrronium cation; therefore, the pharmacological activity of glycopyrrolate is mediated by the active moiety glycopyrronium.

The pharmacology of glycopyrrolate is well understood. Published nonclinical and clinical data have documented the safe use of glycopyrrolate by several routes of administration including oral, intravenous, and topical [9, 10]. The adverse effects associated with glycopyrrolate are generally limited to its pharmacologic actions as an anti-muscarinic agent [11].

Glycopyrronium carries a positive charge and does not readily cross the blood-brain barrier, thus minimizing central nervous system (CNS)-related adverse events (AEs) [12]. Systemic AEs observed with oral dosing include dry mouth, mydriasis, blurred vision, tachycardia, increased ocular tension, and constipation. Topical application may minimize systemic anticholinergic side effects while still preserving efficacy.

Dermira has developed glycopyrronium tosylate, 2.4% as a topically applied product for treatment of primary axillary hyperhidrosis. Full development of glycopyrronium tosylate has been completed with pivotal Phase 3 clinical trials confirming the efficacy and safety of this product in patients with primary axillary hyperhidrosis. Marketing approval in the United States was received in June 2018 and the product is now commercially available as Qbrexza™ (glycopyrronium) cloth, 2.4% for the treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.

1.2 Summary of Investigational Program

Qbrexza (glycopyrronium) cloth, 2.4% is a topical cholinergic receptor antagonist product approved for use in the United States for the treatment of primary axillary hyperhidrosis in adults and children 9 years of age and older.

For a more complete description of all studies refer to the DRM04 Investigator's Brochure.

Study Rationale

Primary palmar hyperhidrosis represents the next most common focal location of hyperhidrosis after axillary hyperhidrosis. Dermira now seeks to understand the efficacy and safety of glycopyrronium cloth, 2.4% in the treatment of primary palmar hyperhidrosis.

2 STUDY SUMMARY

This study will assess glycopyrronium cloth, 2.4% in subjects with primary palmar hyperhidrosis and compare the efficacy and safety of various application methods in order to determine an optimal method for use in palmar hyperhidrosis. The study is intended to assess four application methods (treatment groups) initially. Data from these cohorts will be reviewed and if needed, this protocol will be amended to add one or more treatment groups to assess additional application methods, with the objective of determining optimal conditions for use in palmar hyperhidrosis.

This study is randomized, double-blind, parallel group and vehicle controlled. All subjects will sign an informed consent and undergo screening for study eligibility. Key criteria for entry are diagnosed primary palmar hyperhidrosis for at least 6 months, a hand sweat severity score of ≥4 (NRS 0-10 pts) and an HDSS grade of ≥3 (HDSS grade 1-4). Approximately 60 eligible subjects, ≥9 years of age will be randomized to one of 4 treatment groups at the Baseline visit. Within each treatment group, subjects will be randomly assigned to receive active or vehicle in a 2:1 fashion, respectively. Treatment groups are based on residence time of the drug on the hands and outlined in Table 1.

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Subjects will be instructed on the application method and apply study drug at home once each day for 14 days. Patients will return to the clinic for study visits at Week 1 and Week 2 and will be contacted by phone on Day 4 for safety. Subjects will exit the study at the Week 2 visit. Efficacy measures include a hand sweating severity score (11-pt numerical rating scale (NRS)), gravimetric measurement of hand sweat and the Hyperhidrosis Disease Severity Scale (HDSS). Safety measures include adverse events, local skin reactions (LSRs), vital signs and physical exam, serum chemistry and hematology. Females of child-bearing potential will be tested for pregnancy.

3 STUDY OBJECTIVE

The objective of this study is to assess the efficacy and safety of various application methods for glycopyrronium cloth, 2.4% when used to treat palmar hyperhidrosis.

4 STUDY ENDPOINTS

The primary efficacy endpoint for this trial will be:

- Mean change from Baseline to Week 2 in the hand sweating severity score.

Secondary efficacy endpoints:

- Proportion of subjects who have a ≥3-point improvement in the weekly mean score in hand sweating severity at Week 2.
- Proportion of subjects who have a ≥4-point improvement in the weekly mean score in hand sweating severity at Week 2.

- Proportion of subjects who have a ≥2 grade improvement in HDSS from baseline at Week 2.
- Mean absolute change from baseline in gravimetrically-measured sweat production at Week 2.
- Percent change from baseline in gravimetrically-measured sweat production at Week 2.
- Proportion of subjects who have at least a 50% reduction in gravimetrically measured sweat production from baseline at Week 2.

5 STUDY DESIGN

5.1 Duration of the Study

The duration of the study for each subject is approximately 35 days: up to 21 days in screening and 14 days treatment.

5.2 Study Population and Number of Subjects

Approximately 60 subjects, ≥9 years of age, with primary palmar hyperhidrosis, will be enrolled.

5.3 Selection of Subjects

Subject selection criteria are outlined below. Any questions on the eligibility of a subject for this study must be referred to the Sponsor or their designee, prior to enrollment. No exceptions to inclusion or exclusion criteria will be made.

5.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

1. Signed informed consent and assent (for subjects under legal adult age).
2. Age ≥9 years.
3. Willing to comply with the protocol. Subjects under legal adult age will be assessed by the investigator as to their ability to comply with the protocol.
4. Male or non-pregnant (negative urine pregnancy test in female subjects of child-bearing potential), non-lactating females.
5. Primary palmar hyperhidrosis for at least 6 months duration.
6. Average sweat severity score of ≥4 at Baseline. Subjects must complete at least 4-7 days of the sweat severity NRS within 7 days of randomization.
7. HDSS of 3 or 4 at Baseline.
8. If female and of childbearing potential, subject must be willing to use an accepted method of birth control during study participation and for 30 days after the last study drug application. Females are considered to be of childbearing potential unless surgically sterilized (hysterectomy, bilateral oophorectomy, tubal ligation), have been diagnosed as

infertile, have same gender sex partner, are premenarche or are postmenopausal for at least 1 year. Hormonal contraception exclusively for study participation may be prohibited for minor female subjects according to local law and medical practice.

Acceptable methods of birth control include: abstinence, oral contraceptives, contraceptive patches/implants; injectable contraceptives, double barrier methods (e.g., condom and spermicide) or an intra-uterine device (IUD). Birth control method must have been stable/unchanged for 12 weeks prior to Baseline and must remain unchanged during study participation.

9. If male, is vasectomized or agrees to use an accepted method of birth control with female partner during study participation and for 30 days after the last study drug application. Male subjects must agree not to donate sperm.

5.3.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. Subjects who have taken or are currently taking Qbrexza (glycopyrronium) cloth, 2.4%.
2. Prior surgical procedure for hyperhidrosis.
3. Iontophoresis for the palms within 4 weeks of Baseline.
4. Treatment with botulinum toxin (e.g., Botox®) for palmar hyperhidrosis within 1 year of Baseline.
5. Subjects who are actively participating in an experimental therapy study or who received experimental therapy within 30 days or 5 half-lives (whichever is longer) of the Baseline Visit.
6. Subjects who have had a change in a regimen of psychotherapeutic medication (change in drug, dose, frequency) or who have started a psychoactive medication within two months of randomization.
7. Treatment with medications having systemic anticholinergic activity, centrally acting alpha-2 adrenergic agonists (e.g., clonidine, guanabenz, methyl dopa), or beta-blockers within 4 weeks of the Baseline visit unless dosing has been stable for at least 4 months prior to Baseline and is not expected to change over the course of the study (inhaled anti-cholinergic drugs or beta agonists are allowed).
8. Intravenous (IV), oral, or topical glycopyrrolate treatment or any systemic treatment with an anticholinergic medication such as atropine, belladonna, scopolamine, clindinium or hyoscyamine within 4 weeks prior to Baseline.
9. Current pregnancy or lactation.
10. Open wounds or inflammatory lesions on the hands or, any condition that may alter the barrier function of the skin on the hands.
11. Secondary palmar hyperhidrosis or presence of a condition that may cause secondary hyperhidrosis (e.g., lymphoma, malaria, severe anxiety not controlled by medication, carcinoid syndrome, substance abuse, hyperthyroidism).

12. Screening clinical chemistry or hematology laboratory value that is considered clinically significant, in the opinion of the Investigator.
13. Known history of Sjögren's syndrome or Sicca syndrome.
14. History of glaucoma, inflammatory bowel disease, toxic megacolon, active febrile illness, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis or myasthenia gravis.
15. Men with a history of urinary retention requiring catheterization due to prostatic hypertrophy or severe obstructive symptoms of prostatic hypertrophy.
16. History or presence of ventricular arrhythmias, atrial fibrillation, atrial flutter. History of other supraventricular tachycardia with a ventricular rate greater than 100 (other than sinus tachycardia).
17. Subjects who are a poor medical risk because of other systemic diseases or active uncontrolled infections, or any other condition which, in the judgment of the Investigator, would put the subject at unacceptable risk for participation in the study.

6 STUDY DRUG

6.1 Medicinal Product

Study drug, for this trial, will be supplied as glycopyrronium cloth, 2.4 % and vehicle cloth.

Glycopyrronium is formulated as a 2.4 % hydroethanolic solution containing glycopyrronium tosylate, citric acid (anhydrous), sodium citrate dihydrate, purified water and dehydrated alcohol. The solution is a clear, colorless to pale yellow liquid. Each active cloth contains a total of 105 mg glycopyrronium tosylate.

Vehicle solution has the same appearance and contains the same excipients with the exception of the active ingredient, glycopyrronium.

Active and vehicle solutions are applied using a pre-saturated 100% polypropylene, nonwoven, fabric cloth.

6.2 Packaging, Labeling and Storage

Study drug is packaged in individual foil pouches for single-use application. Active and vehicle cloths and foil pouches are identical in appearance.

Study sites will be supplied with weekly cartons for each subject enrolled. Each carton will contain 9 pouches, allowing for 7 days of study drug application plus extra pouches to allow for flexibility with the visit schedule. For the initial four cohorts, each subject will receive one carton at the Baseline visit and one carton at the Week 1 visit.

Study drug pouches and cartons will be labeled with the study number, a unique carton number, contents, storage conditions, manufacturer and Sponsor information, precautionary statements and expiry date if applicable. Study drug labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

Study drug is to be stored at ambient temperature (15–30°C) in a secure, locked facility accessible only to authorized study personnel. Do not freeze or expose wipes to heat or store the drug product at high temperatures. This drug product is flammable. Avoid fire, flame, or smoking during and immediately following application.

6.3 Treatment Assignment

Randomization and IWRS

At the Baseline visit, qualified subjects will be randomized to treatment using an Interactive Web-based Randomization System (IWRS). The IWRS will assign a study drug carton number. The carton number will be recorded in the eCRF.

Subjects will be randomized to treatment groups by Age groups: Age <= 12 years and Age > 12 years in such a manner to balance treatment allocation across the entire study.

Study Blinding

The Sponsor, the CRO, the Investigator, study site personnel and subjects will be blinded to treatment assignment (active or vehicle).

The integrity of this clinical study must be maintained by observing the treatment blind. If an adverse event occurs which cannot be managed without knowing whether the subject is receiving active study drug or vehicle solution, the IWRS system will be used to obtain treatment assignment information. The Medical Monitor must be notified whenever study medication is unblinded, preferably prior to unblinding a subject.

6.4 Study Drug Dispensing and Return

It is the responsibility of the Investigator to ensure that study drug is only used on subjects enrolled in this study. The study drug must only be dispensed from study sites by authorized personnel according to the protocol and local regulations.

Study drug will be dispensed by the study site to the subject at each study visit. Subjects are to return all study drug pouches (used and unused) to the study site. The pouches will be counted prior to dispensing and upon return and the counts will be recorded in the source documents and eCRF.

Each subject is to be instructed on the importance of returning study drug at the next study visit. If a subject does not return study drug, they will be instructed to return it as soon as possible. If under legal adult age the parents/legal representatives will also be instructed on the importance of returning study drug. The site staff will visually inspect the pouches to ensure product usage is consistent with the subject's e-diary.

6.5 Study Drug Application

Subjects will be instructed on the application of the study drug and will demonstrate proper application technique in the clinic using a vehicle cloth, timer and non-latex glove, where occlusion is specified. For treatment groups where occlusion is specified, the study site should

select a non-latex glove size (e.g., small, medium, large) that ensures a snug fit on the hand. Subjects will be provided all supplies in order to properly apply study drug at home.

Study drug should be applied to clean, dry skin. A single wipe will be used to apply study drug to both hands once daily, in the evening (i.e., before bedtime).

The subject will be instructed to apply the study drug as follows:

Treatment Group	Application Method	Subject Instructions
1	15 minutes residence time wearing non-latex gloves	1. Tear open the top of the pouch at the notch. 2. Remove the wipe from the pouch and unfold the wipe. 3. Wipe one hand once. 4. Using the same wipe apply the study drug to the other hand. 5. Return the wipe to the pouch. 6. Allow study drug to dry for approximately 5 minutes 7. Put gloves on both hands. 8. Set timer for 15 minutes. 9. After 15 minutes, remove gloves and discard. 10. Thoroughly wash hands with soap and water.
2	30 minutes residence time wearing non-latex gloves	1. Tear open the top of the pouch at the notch. 2. Remove the wipe from the pouch and unfold the wipe. 3. Wipe one hand once. 4. Using the same wipe apply the study drug to the other hand. 5. Return the wipe to the pouch. 6. Allow study drug to dry for approximately 5 minutes. 7. Put gloves on both hands. 8. Set timer for 30 minutes. 9. After 30 minutes, remove gloves and discard. 10. Thoroughly wash hands with soap and water.
3	15 minutes residence time	1. Tear open the top of the pouch at the notch. 2. Remove the wipe from the pouch and unfold the wipe. 3. Wipe one hand once. 4. Using the same wipe apply the study drug to the other hand. 5. Return the wipe to the pouch. 6. Allow study drug to dry for approximately 5 minutes. 7. Set timer for 15 minutes. 8. Do not touch anything during the 15 minute wait time. 9. After 15 minutes, thoroughly wash hands with soap and water.
4	30 minutes residence time	1. Tear open the top of the pouch at the notch. 2. Remove the wipe from the pouch and unfold the wipe. 3. Wipe one hand once. 4. Using the same wipe apply the study drug to the other hand. 5. Return the wipe to the pouch. 6. Allow study drug to dry for approximately 5 minutes. 7. Set timer for 30 minutes. 8. Do not touch anything during the 30 minute wait time. 9. After 30 minutes, thoroughly wash hands with soap and water.

Subjects should avoid any contact with the eyes or mouth. Subjects should avoid fire, flame, or smoking during and immediately following application.

There will be a planned total of 14 applications of study drug for the study. Missed doses should be applied provided there is a 12-hour window until the next scheduled dose.

6.6 Treatment Compliance

Treatment compliance will be assessed at each visit using a subject-completed e-diary and visual inspection of the pouches. Subjects will be instructed to bring all study drug pouches, wipes (used and unused) and diaries to the next study visit.

A subject deviating significantly from the daily dosing regimen will be counseled.

The first and last dates of study drug usage and any missed applications will be recorded in the appropriate eCRF.

6.7 Study Drug Accountability

The Investigator or designee will be responsible for documenting drug accountability at the site. Study drug accountability records will document the receipt, dispensing and return of study drug and provide a complete account of all used and unused study drug. Study drug accountability records will be reviewed regularly throughout the study by the Sponsor/designee. Study drug will be returned to the Sponsor or designee at the end of the study, following final study drug accountability.

7 CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (including over-the-counter drugs, vitamins, antacids, any agent that promotes drying, and skin care products used on the hands) taken during screening and throughout the study will be recorded in the eCRF.

Medication entries should be specific to the generic name (if a combination drug, then marketed product name) and will include the dose, unit, and frequency of administration and/or treatment, route of administration, start date, discontinuation date, and indication.

The Investigator should examine the acceptability of all concomitant procedures, medications, topical preparations and dietary supplements not explicitly prohibited in this study.

In order to ensure that appropriate concomitant therapy is administered, subjects will be instructed to consult with the Investigator prior to taking any medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician).

7.1 Permitted Treatments and Procedures

The use of concomitant medications for medical conditions (e.g., hypertension, diabetes, acute infections) or treatment of an adverse event is permitted during this study as long as medications are not explicitly prohibited by the protocol.

7.2 Prohibited Treatments and Procedures

Subjects should not undergo any elective medical procedure without prior consultation with the Investigator. Elective out-patient procedures (e.g., minor outpatient surgery) that might require hospitalization or anesthesia should be deferred until after the study, whenever clinically appropriate. However, subjects may continue in the study if not contraindicated by the procedure or if continuation is not deemed in the subject's best interest.

The following medications and treatments are prohibited during the study:

- Concomitant treatment for palmar hyperhidrosis (e.g., palmar iontophoresis [iontophoresis for other areas affected by hyperhidrosis are allowed]).
- Any anticholinergic drug and/or initiation of change in dose of medications with centrally acting alpha 2 adrenergic agonists (e.g., clonidine, guanabenz, methyl dopa), or beta-blockers.
- Intravenous (IV), oral or topical glycopyrrolate treatment.
- Any agent that promotes palmar drying (e.g., powders).

8 STUDY PROCEDURES

The procedures required for subject evaluation at each study visit are outlined below and in the study Schedule of Visits and Procedures. See Protocol Appendix B. The timing of each study day is relative to the day of initial dosing (Day 1/Baseline). Visit windows are provided to allow study sites some flexibility in maintaining the study visit schedule for participating subjects. Out of window visits may be unavoidable in certain circumstances. Out of window visits are not considered deviations to the protocol.

8.1 Screening Period (Day -21 to -1)

The screening evaluation period may take up to 21 days in order to provide adequate washout time for subjects taking certain medications. The purpose of the screening visit is to ensure that appropriate subjects are entered into the study and remain stable during the pre-treatment period. Questions on eligibility will be referred to the Sponsor or their designee. Screen failures may be re-screened once at any time, and must be assigned a new screening number as described in Section 5.3. Screen failure information will be recorded in the eCRF. Screening procedures, excluding lab evaluations, may be done any time during the screening period (prior to dosing on Day 1) and after the subject has given informed consent.

- Obtain written informed consent
- Collect demographic information
- Complete medical history/review of systems
- Review inclusion/exclusion criteria
- Query subject for prior and concomitant medication use

- Perform a complete physical examination
- Record height and weight
- Measure vital signs
- Draw blood samples for laboratory tests. Collect urine pregnancy test
- Dispense electronic diary and instruct on use
- Schedule next visit

8.2 Baseline Visit (Day 1)

- Collect concomitant medication information
- Measure vital signs
- Update medical history
- Conduct urine pregnancy test
- Evaluate hands for local skin reactions (see Section 9.3.4)
- Confirm HDSS (see Section 9.2.3)
- Conduct gravimetric measurement of sweat production for each hand (see Appendix A)
- Confirm subject eligibility and randomize to treatment
- Train subject on application method and dispense study drug
- Schedule next visit

8.3 Day 4 (+ 1 day)

- Telephone call for adverse events

8.4 Week 1 (+/-1 day)

- Collect concomitant medication information
- Measure vital signs
- Review and record AEs
- Evaluate hands for local skin reactions (see Section 9.3.4)
- Conduct gravimetric measurement of sweat production for each hand (see Appendix A)
- Review compliance/count pouches and dispense drug
- Verify e-diary is complete
- Dispense study drug
- Schedule next visit

8.5 Week 2 (+/-1 day)

- Collect concomitant medication information
- Measure vital signs
- Conduct physical exam
- Record weight
- Review and record AEs
- Draw blood samples for laboratory tests. Collect urine pregnancy test
- Evaluate hands for local skin reactions (see Section 9.3.4)
- Conduct gravimetric measurement of sweat production for each hand (see Appendix A)
- Verify e-diary is complete
- Review treatment compliance/count pouches and collect all study medication

8.6 Unscheduled Visits

Additional visits will be scheduled as necessary to ensure the safety and well-being of subjects who experience AEs. Laboratory evaluations, if necessary, will be collected and analyzed using the central laboratory for this study. Data will be recorded in the eCRF.

9 DETAILS OF ASSESSMENTS

Parental assistance for study drug application and study conduct procedures may be needed for younger subjects qualifying for study participation.

9.1 Screening Assessments

9.1.1 Demographics

At the screening visit, demographic information including age, gender, race and ethnicity will be collected and recorded in the eCRF for each subject.

9.1.2 Medical History

A complete medical history will be collected as part of the screening assessment and include all clinically relevant past or coexisting medical conditions or surgeries. The medical history will be updated prior to treatment on Baseline/Day 1 should new findings be present since the screening visit.

Findings will be recorded in the eCRF.

9.1.3 Disease Specific Information

Information on the subject's palmar hyperhidrosis will be collected as part of the screening assessment and include the date of onset, anatomical areas affected by hyperhidrosis, including the hands, family history, and past treatments used for hyperhidrosis. Information will be recorded in the eCRF.

The investigator will assess skin thickness on the palms and information on sweat triggers, duration and episodes per day will be collected.

9.2 Assessment of Efficacy

9.2.1 Patient Reported Outcomes

All subjects will be provided with an electronic diary (e-diary) used to complete 4 patient reported outcome measures as described below. The items will be collected in the evening and automatically prompted for subject response.

The study site will monitor the subject's compliance in completing the items and contact any subject not using the electronic diary daily. Subjects must return the electronic diary at the end of the treatment period.

e-Diary data will be transferred electronically to the study database.

9.2.1.1 Hand Sweat Severity

The hand sweat severity item is a patient reported outcome, collected daily, which is designed to measure the severity of palmar hyperhidrosis. This item will be completed by subjects ≥16 years of age. A children's version of the hand sweat severity item will be completed by subjects <16 years of age.

During the screening period, subjects must complete the daily items for at least 4 days within the 7-day screening period, prior to randomization. Subjects randomized into the trial must have an average hand sweating severity score of at least 4 at Baseline, to be eligible for study participation.

Subjects randomized into the trial will continue to complete the items daily, in the evening, during the clinical trial.

9.2.2 Impact and Bother

Subjects ≥16 years old will complete two items, daily, which ask the subject to assess the impact of their palmar sweating on their activities and how bothered they are by their palmar hyperhidrosis.

9.2.3 Hyperhidrosis Disease Severity Scale (HDSS)

The HDSS (Appendix C) is a disease-specific diagnostic tool that provides a qualitative measure of severity of the subject's sweating based on how sweating affects daily activities. The subject will select the HDSS grade that best describes their disease.

9.2.3.1 Global Impression of Change

Subjects will be asked once, at the end of study, for an overall impression of their hand sweating compared to before treatment.

9.2.4 Gravimetric Measurement of Sweat Production

The details of the gravimetric procedure are specified in Appendix A. All equipment and supplies for conducting the gravimetric procedure will be provided to the study site. Study sites will be provided with a source document template for recording all information regarding the gravimetric procedure. Sites will be trained on the gravimetric procedure prior to starting the study, by the Sponsor or designee.

Gravimetric data will be entered in the eCRF.

9.3 Assessment of Safety

9.3.1 Physical Examination

A complete physical examination will be conducted and cover general appearance, dermatological, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal, and lymphatic body systems. Height and weight will be recorded as part of the screening physical exam and only the subject's weight will be recorded with the end of study physical exam. Findings will be recorded in the eCRF.

9.3.2 Vital Signs

Vital signs, including body temperature, respiratory rate (breath per minute), pulse (beats per minute), and blood pressure (mmHg), will be obtained with the subject in the seated position, after sitting for at least 5 minutes. Any abnormal findings which are new or worsened in severity and clinically significant, in the opinion of the Investigator, will be recorded as an AE. Vital sign measurements will be recorded in the eCRF.

9.3.3 Laboratory Evaluations

Laboratory tests will be collected to evaluate safety in all study subjects and analyzed using a central laboratory. Labs will be collected per the Schedule of Visits and Procedures (see Appendix B) or as clinically indicated. Laboratory samples are to be shipped on the same day as collected. No more than 21 mLs will be collected over 2 scheduled visits in subjects under the legal adult age. Laboratory tests are described below.

Hematology: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell count and differential (%), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume, RBC morphology, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils.

Chemistry: sodium, potassium, chloride, calcium, phosphorus, bicarbonate, uric acid, blood urea nitrogen (BUN), creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin (total and direct), and non-fasting glucose.

Urine pregnancy testing (beta human chorionic gonadotropin [β-hCG]) will be performed at the Screening, Baseline/Day 1, and the Week 2/Early Withdrawal visit for all females unless post-menopausal/sterile.

Screening laboratory values must be reviewed by the Investigator prior to subject enrollment. Subjects will be screen failed for clinically significant laboratory values. Screening laboratory tests may be repeated one time in order to confirm out of range results or clinical significance, at the discretion of the investigator.

The central laboratory should be used for any laboratory testing required for a subject during study participation, including laboratory testing needed for unscheduled visits. Clinically significant laboratory results must be recorded on the adverse event eCRF, preferably as a diagnosis rather than individual test results. Any subject who has a clinically significant laboratory test result will be evaluated by the PI, and will be treated and/or followed up at the discretion of the PI until the value returns to clinically acceptable levels.

9.3.4 Local Skin Reactions

All subjects will be assessed for Local Skin Reactions (LSRs). LSRs include burning/stinging, pruritus, edema, erythema, dryness and scaling. Each LSR will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe). LSRs observed on a study visit day are not recorded as adverse events unless scored as 3 (Severe). Local skin reactions experienced by the subject in between study visits are to be recorded as an AE.

Burning/stinging and pruritus will be assessed by the subject and edema/swelling, erythema, dryness and scaling will be assessed by the Investigator/designee. Subjects will be read the definition of each subject-assessed LSR and asked to select the appropriate definition. The corresponding grade will be assigned by the site and entered in the eCRF.

Table 1: Subject Assessed Local Skin Reactions

Score	Grade	Burning/Stinging	Pruritus
0	None	No stinging/burning	No pruritus
1	Mild	Slightly warm, tingling sensation; not really bothersome	Occasional, slight itching/scratching
2	Moderate	Definite warm; tingling/stinging sensation that is somewhat bothersome	Intermittent itching/scratching which does not disturb sleep
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort	Bothersome itching/scratching which disturbs sleep

Table 2: Investigator Assessed Local Skin Reactions

Score	Grade	Edema	Erythema	Dryness	Scaling
0	None	No edema	No erythema present	None	None
1	Mild	Slight, barely perceptible edema	Slight erythema: very light-pink	Perceptible dryness with no flakes or fissure formation	Slight diffuse scaling
2	Moderate	Distinct presence of edema	Dull red, clearly distinguishable	Easily noted dryness and flakes but no fissure formation	Diffuse scaling
3	Severe	Marked, intense edema	Deep/dark red	Easily noted dryness with flakes and fissure formation	Prominent, dense scaling

9.3.5 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a study drug in humans, whether or not considered drug related. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study drug, whether or not related to the investigational product.

Adverse events (AEs) will be monitored throughout the study. Subjects will be instructed to inform the Principal Investigator (PI) and/or study staff of any AEs. At each visit, subjects will be asked about AEs in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been since the last visit?). Specific inquiry regarding reported AEs will be conducted when applicable. All adverse events will be documented and recorded in the subject's eCRF.

Any subject who has an AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the PI, and will be treated and/or followed up until the symptoms or values return to normal or to clinically acceptable levels, as judged by the PI. A physician, either at clinical site, or at a nearby hospital emergency room, will administer

treatment for any serious adverse events (SAEs), if necessary. When appropriate, medical tests and examinations will be performed to document resolution of event(s).

9.3.5.1 Reporting

Only AEs that occur during or following study treatment with the drug will be reported in the AE section of the eCRF. Events recorded prior to study treatment with the drug will be reported in the Medical History section of the eCRF as appropriate. All AEs occurring during the course of the study will be individually recorded in the eCRF. A condition that is present prior to administration of study drug and that worsens after administration of study drug should be reported as an AE. Information regarding the onset, duration, severity, action taken, outcome, and relationship to study drug will be recorded.

New or worsening abnormal laboratory values and/or vital signs are to be recorded as AEs if they are considered to be of clinical significance by the PI or meet the criteria of an SAE as described in Section 9.3.6.

Unless a diagnosis is available, signs and symptoms must be reported as individual AEs in the eCRF; a diagnosis is preferred.

The severity of an AE will be designated as mild, moderate or severe. The term "severe" is used to describe the intensity of an adverse event; the event itself, however, may be of relatively minor clinical significance (e.g. 'severe' upper respiratory infection). Severity is not the same as "serious". Seriousness of AEs is based on the outcome/action of an AE.

The relationship of the AE to the study treatment will be based on the following two definitions:

Not related: An AE is defined as "not related" if the AE is not judged to be associated with the study drug and is attributable to another cause;

Related: An AE is defined as "related" where a causal relationship between the event and the study drug is a reasonable possibility (possibly or probably related). A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/ rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

9.3.6 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose,

- Results in death;
- Is immediately life-threatening (i.e., in the opinion of the PI, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death);
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;

- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

As soon as the PI becomes aware of an AE that meets the criteria for an SAE, the SAE should be documented to the extent that information is available. A report must be submitted by the study site to the Sponsor or designee, within 24 hours.

Any SAE, regardless of causal relationship, must be reported to the Sponsor immediately (within 24 hours of the PI's knowledge of the event). Forms for reporting SAEs will be provided to the study site.

SAEs will be recorded from the time of informed consent, through to end of the study. If in the opinion of the Investigator, an SAE occurring outside the specified time window (i.e., following subject completion or withdrawal from the study), is deemed to be drug-related, then the event should be reported within 24 hours as outlined above.

The Investigator should institute any clinically necessary supplementary investigation of SAE information. In the case of subject death, any post-mortem findings/reports will be requested.

9.3.6.1 Reporting Serious Adverse Events

All SAEs, as defined by the criteria above, must be reported to the Sponsor or designee using the SAE Form provided, within 24 hours of the study staff becoming aware of the event.

Serious adverse events must be recorded on an SAE report form. The minimum information required for SAE reporting includes the identity of the PI, site number, subject number, event description, SAE term(s), reason why the event is considered to be serious (i.e., the seriousness criteria), and PI's assessment of the relationship of the event to study drug. Additional SAE information including medications or other therapeutic measures used to treat the event, and the outcome/resolution of the event should also be recorded on the SAE Reporting Form.

In all cases, the PI should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. The Investigator may be required to provide supplementary information as requested by the Sponsor or its designee.

When reporting SAEs, the following additional points should be considered:

- When the diagnosis of an SAE is known or suspected, the PI should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms; signs, symptoms and tests that support the diagnosis should be provided.
- Death should not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. If an autopsy was performed, the autopsy report should be provided.

While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:

- Hospitalization for elective or previously scheduled surgery or procedure for a pre-existing condition that has not worsened after administration of study drug (e.g., a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
- Events that result in hospital stays for observation only of fewer than 24 hours and that do not require admission or therapeutic intervention/treatment (e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).

The Sponsor will process and evaluate all SAEs as soon as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor will assess the expectedness of each SAE to the study treatment. The current Investigator's Brochure will be used as the reference document to assess expectedness of the event to study drug.

9.3.7 Dosing Changes Due to AEs

Dose interruptions are allowed should a subject experience intolerable treatment-related adverse events (e.g., dry mouth) on study. In cases where the Investigator feels a dose interruption is warranted, the subject should be instructed to interrupt study drug application for 1 - 2 days to allow symptoms to resolve and then be returned to once daily dosing. If subject is unable to restart medication after a maximum of a two day hold or if the subject cannot tolerate the once daily regimen after study drug is restarted the subject should be withdrawn.

Dosing interruptions are to be recorded in the e-diary as a missed dose.

9.3.8 AEs of Special Interest

The Sponsor or designee must be contacted if a subject experiences treatment-related blurred vision or has treatment-related symptoms associated with urinary hesitancy, obstruction or retention. Study drug will be discontinued immediately until symptoms abate. Additional data will be collected for AEs of special interest in real time and sent to the company within 48 hours of reporting the AE. Forms for this purpose will be provided to the study site.

Subjects who complain of blurred vision should be carefully evaluated to determine if the subject inadvertently touched the eye(s) after application of study drug. If there is no history of inadvertent introduction of study drug into the eye, the subject should be evaluated to rule out any serious acute condition. If the blurred vision continues for more than 48 hours, the subject should be evaluated by an ophthalmologist or referred to an emergency room as soon as possible.

Subjects who have signs and/or symptoms suggestive of acute glaucoma should be referred to an ophthalmologist or emergency department immediately.

Subjects who have symptoms suggestive of urinary retention should be questioned regarding its clinical course. If the subject has symptoms of frank obstruction the subject should be evaluated immediately by a urologist or referred to an emergency room and study drug should be discontinued.

Dose changes due to blurred vision or symptoms of urinary obstruction should be discussed with the Medical Monitor.

The subject's source document must include any follow-up information regarding blurred vision and urinary retention and must be followed until resolution.

Study drug must be discontinued if an adverse event is deemed persistent and if continuation of study drug would not be in the best interest of the subject.

Refer to Section 10.3 for further information regarding discontinuation of study drug or early withdrawal.

9.3.9 Pregnancy

Should a subject become pregnant during study participation, study drug dosing will be discontinued and the subject will be withdrawn from study. The Investigator must perform medical assessments as clinically indicated and continue to follow the subject for at least 4 weeks after delivery. Details for both the mother and baby must be obtained. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The Investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy. Pregnancy reporting forms will be provided to the study site.

10 STUDY DISCONTINUATIONS

10.1 Discontinuation of the Study

The Sponsor has the right to terminate or to stop the study at any time. Should this be necessary, both the Sponsor and the Investigator will ensure that proper study discontinuation procedures are completed. The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigators at each site with the concurrence of the sponsor or the sole opinion of the Sponsor, makes the continuation of the study unnecessary or unethical.
- The stated objectives of the study are achieved.
- The Sponsor discontinues the development of the study drug.

Regardless of the reason for withdrawal, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

10.2 Early Withdrawal of Study Subjects

The Investigator will make every reasonable effort to keep each subject in the study; however, a subject may voluntarily withdraw from study participation at any time. If the subject withdraws consent and discontinues from the study, the Investigator will attempt to schedule an Early Withdrawal Visit as soon as possible, determine the reason for discontinuation, and record the reason in the subject's study records and in the eCRF.

If at any time during the study, the Investigator determines that it is not in the best interest of the subject to continue, the subject will be discontinued from participation. The Investigator can discontinue a subject at any time if medically necessary. The Investigator may discontinue a subject's participation if the subject has failed to follow study procedures or to keep follow-up appointments. Prior to discontinuing a subject from study participation, the Investigator will discuss his/her intentions with the Sponsor Medical Monitor or designee. Appropriate documentation in the subject's study record and eCRF regarding the reason for discontinuation must be completed.

All subjects who fail to return to the study center for the required follow-up visits will be contacted by phone to determine the cause(s) why the subject failed to return for the necessary visit or elected to discontinue from the study. If a subject is unreachable by telephone after a minimum of two documented attempts (one attempt on two different days), a registered letter will be sent requesting that subject contact the site regarding study follow-up.

Subjects will be discontinued early from the study if any of the following occur:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment and/or participation in the study is not in the best interest of the subject.
- Death.
- Serious protocol violation, including persistent non-compliance or subject requiring medication or procedures prohibited by the protocol, to allow subjects to receive the appropriate medical attention. In such cases, the Investigator must contact the Sponsor or designee, as the final decision to withdraw the subject will be taken by the Sponsor.
- Discontinuation of the study by the Sponsor.

10.3 Study Drug Discontinuation

For subjects who decide to prematurely discontinue study drug treatment, all reasonable efforts should be made to obtain all protocol-specified safety assessments and end of study procedures.

The Investigator should stop study drug treatment in the following instances:

- Inter-current illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree.

- Any clinical adverse event which is clinically significant, is deemed persistent, is probably or definitely related to study drug in the judgment of the Investigator.

11 STATISTICAL CONSIDERATIONS

11.1 General Statistical Methodology

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum and maximum. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

As a sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points).

Demographic data will be summarized by treatment group using descriptive statistics. Subjects' Baseline characteristics related to efficacy analyses will be compared with descriptive statistics among treatment groups to ensure comparable results.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal during the blinded study will be summarized using frequencies and percentages by treatment group.

Sweat production will be measured gravimetrically for each hand at each time point. Analyses of sweat production will be based on the mean of the right and left hand measurements.

Subjects are to complete the hand sweating severity item #1 each night during the clinical trial. The mean of each subject's responses to item #1 will be computed for each week, weekly mean response to item #1 will be analyzed. The weekly mean will be calculated if a subject has responses to item #1 on at least 4 of the 7 days of the week. If the subject has 3 or fewer responses to item #1, the value will be considered missing.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

11.1.1 Populations Analyzed

Approximately 60 subjects (including subjects ≥9 years) will be randomized to glycopyrronium cloth, 2.4% or vehicle treatment groups in a 2:1 ratio. Efficacy analyses will be performed using the intent-to-treat (ITT) population and the per-protocol (PP) population. Safety analyses will be performed using the safety population.

All subjects who are randomized and dispensed study drug will be included in the ITT population.

All subjects who are randomized and receive at least one confirmed dose of study drug will be included in the safety population.

The PP population will include all subjects in the safety population who complete the Week 2 evaluation without any significant protocol violations (i.e., any subject or Investigator activity that could have possibly interfered with the therapeutic administration of the study drug or the precise evaluation of treatment efficacy). The PP population will include subjects in the safety population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Used an interfering concomitant medication or underwent a prohibited procedure;
- Did not attend the Week 2 visit;
- Missed both the Week 1 and Week 2 visit;
- Have not been compliant with the dosing regimen (i.e. subjects must apply 80−120% of the expected applications of study medication during participation in the study);
- Out of visit window at the Week 2 visit by more than ±2 day;

Subjects that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the PP population. Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

11.1.2 Primary Efficacy

The primary endpoint will be analyzed:

- Mean change from Baseline to Week 2 in the hand sweating severity score

Each active treatment group will be compared to its corresponding vehicle group using the Wilcoxon Rank-sum nonparametric test and the two sample t-test.

11.1.3 Secondary Efficacy

For the secondary efficacy endpoints:

- Proportion of subjects who have a ≥3-point improvement in the weekly mean score in hand sweating severity at Week 2.
- Proportion of subjects who have a ≥4-point improvement in the weekly mean score in hand sweating severity at Week 2.
- Proportion of subjects who have a ≥2 grade improvement in HDSS from baseline at Week 2.

- Mean absolute change from baseline in gravimetrically-measured sweat production at Week 2.
- Percent change from baseline in gravimetrically-measured sweat production at Week 2.
- Proportion of subjects who have at least a 50% reduction in gravimetrically measured sweat production from baseline at Week 2.

Each active treatment group will be compared to its corresponding vehicle group using Fisher's Exact Test.

For the secondary efficacy endpoint:

- Mean absolute change from baseline in gravimetrically-measured sweat production at Week 2.

Each active treatment group will be compared to its corresponding vehicle group using the Wilcoxon rank-sum nonparametric test and the two sample t-test.

No imputation of missing values will be performed. The observed data will be analyzed.

Subjects 16 years or older will be asked to provide answers to items 2, 3 and 4.Tabulations of their data will be based on the following methodology. Daily Diary (DD) contains a set of diary items designed to measure the severity and impact of any hand sweating collected daily wherein the evaluation is focused on the past 24 hours.

The categorical values of the daily diary questions 2 and 3 relating to their experience within the previous 24-hour period, including nighttime hours will be assigned a numerical value wherein the lower assignments will represent a more favorable outcome. A weekly average will be created for each subject for questions 2 to 3. Question 4 is designed to capture subject's global impression of change and is only collected at end of treatment (EOT) visit.

The scoring of each answer for questions 2 and 3 is as follows:

Q2 / Q3: Not at all / Not at all bothered	scored 0
Q2 / Q3: A little bit / A little bothered	scored 1
Q2 / Q3: A moderate amount / Moderately bothered	scored 2
Q2 / Q3: A great deal / Very bothered	scored 3
Q2 / Q3: An extreme amount / Extremely bothered	scored 4

Subjects will complete the DD for 4-7 days within 7 days of randomization during the screening period. Daily data will be averaged and used to compute baseline scores. Baseline DD scores will be calculated as follows:

- Baseline scores for items 2 and 3: The most recent 7 days prior to randomization day (Day 1) will be averaged to calculate the baseline scores for items 2 and 3. If a subject has complete DD records for less than 7 days prior to Day 1, then the average will be calculated based on all available records before Day 1.

The weekly average will be calculated for items 2 and 3. If a subject misses more than 4 days of DD records within a week, the weekly average of questions 2 and 3 will be considered as missing. The absolute change in the weekly average for questions 2 and 3 from Baseline to Week 4 by visit will be summarized by group using descriptive statistics. Weekly average scores for questions 2 to 3 will also be presented.

Responses to 4 will be summarized in a frequency table by visit and treatment group.

11.1.4 Sensitivity Efficacy Analyses

11.1.4.1 Analyses Using Last Observation Carried Forward

In the sensitivity analysis, missing values will be imputed using LOCF. Each primary and secondary endpoint will be analyzed as it was in the primary analyses. For absolute change from baseline to Week 2 in gravimetrically-measured sweat production, each active treatment group will be compared to its corresponding vehicle group using the Wilcoxon rank-sum nonparametric test and two sample t-test. For efficacy variables that are proportions, each active treatment group will be compared to its corresponding vehicle group using Fisher's Exact test.

Gravimetrically-measured sweat production will be analyzed with the Wilcoxon rank-sum nonparametric test and two sample t-test.

11.1.5 Subgroup Analyses

No subgroup analyses are planned.

11.1.6 Exposure and Compliance

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of applications, number of missed applications and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the expected number of applications while enrolled in the study.

11.1.7 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first study drug application. Adverse events noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

All information pertaining to an AE noted during the study will be listed by subject, detailing the verbatim term given by the Investigator or designee, preferred term, system organ class, onset date, resolution date, severity, seriousness, action taken, outcome and drug relatedness. The event onset will also be shown relative (in number of days) to date of first application.

Treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting a TEAE, system organ class, preferred term, severity, relationship to study drug (causality) and seriousness. When summarizing AEs by severity and relationship, each subject will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs will be summarized by treatment group, severity and relationship to study drug, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

11.1.8 Local Skin Reactions

Local Skin Reactions (LSRs) include burning/stinging, pruritus, edema/swelling, erythema, dryness and scaling. LSRs will be scored as 0 (None), 1 (Mild), 2 (Moderate) or 3 (Severe). LSRs will be summarized by treatment group and visit using descriptive statistics. A by-subject listing of subjects with any LSR of 3 will be presented.

11.1.9 Other Safety Data

Laboratory test results will be summarized descriptively at baseline and Week 2. Additionally, shifts from baseline to Week 2 in laboratory test results based on normal ranges will be summarized with descriptive statistics. Individual laboratory test results will be presented in a by-subject listing. Any clinically significant laboratory abnormalities will be captured as adverse events.

Vital signs will be presented by treatment group as observed values and changes from baseline using descriptive statistics.

Medical histories will be coded using the MedDRA dictionary and presented in a by-subject listing.

Concomitant medications will be coded using the WHO-Drug dictionary. Concomitant medications will be summarized by treatment, drug class and preferred term.

Physical examination data will be presented in a by-subject listing.

11.1.10 Sample Size Determination

The sample size for this study was based mainly on clinical considerations.

12 STUDY ADMINISTRATION

12.1 Compliance with the Protocol

The study shall be conducted as described in this protocol. All revisions to the protocol must be prepared by the Sponsor. The Investigator will not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/EC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

Any significant deviation must be documented and submitted to the IRB/EC; the Sponsor or designee; and, if required, Regulatory Authority(ies).

Documentation of approval signed by the chairperson or designee of the IRB(s)/EC(s) must be sent to the Sponsor and/or designee.

12.2 Informed Consent Procedures

The Informed Consent Form (ICF) and Assent Forms for subjects under legal adult age must include all elements required by ICH/GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. For subjects under legal adult age, both parents or legal representative may be required to sign informed consent as applicable. Assent to participate in a clinical trial applies to all subjects who are not legal adult subjects (in the state or location in which they are participating) and is defined as a child's affirmative agreement to participate in research. Permission of the minor subject's parent or legal guardian must also be obtained in compliance with part 50, subpart B of the Code of Federal Regulations and must include the elements of informed consent as described in Section 50.21 and according to the regulations where the study is being conducted. Appropriate ICFs and assent forms will be provided according to local law/regulations. If a subject reaches legal adult age during the course of the trial, an adult ICF will be signed.

The ICF and Assent Forms must also include a statement that the Sponsor and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/EC's written approval/favorable opinion of the written ICF, Assent Forms and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be nontechnical and easily understood. The Investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then the ICF must be signed and personally dated by the subject or the subject's legally acceptable representative, by the Investigator and by the person who conducted the informed consent discussion as required by local law. The subject or legally acceptable representative should receive a copy of the signed ICF and any other written information provided to study subjects prior to subject's participation in the study. This also applies to Assent Forms. All subjects and/or the legally acceptable representative (i.e. parents or guardian) will be provided with a contact address where they may obtain further information regarding the study.

The ICF, Assent Forms and any other information provided to the subjects or the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/EC approval/ favorable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication to the subject should be documented in the source note (proforma).

During a subject's participation in the study, any updates to the consent or assent forms and any updates to the written information will be provided to the subject.

12.3 Study Documentation and the Case Report Form

The Investigator is responsible for ensuring that data are properly recorded in the eCRFs and on related documents. All entries must be supported by the subject's medical records or source notes. The Investigator who has signed the protocol signature page is to ensure that the observations and findings are recorded correctly and completely.

All Investigator observations/assessments must be reported in the eCRF. The original reports and any traces and films must be reviewed, signed and dated and retained by the Investigator for future reference.

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation. Data reported in the eCRFs that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator must certify that the data are complete and accurate at the time the subject ends the study or as instructed by the Sponsor or designee by applying an electronic signature to the eCRF study completion page.

12.4 Study Monitoring

The Sponsor or designee will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study. The study monitor will verify adherence to the protocol and completeness, consistency and accuracy of the data by comparing subjects' source documents with entries in the eCRF. The study monitor must be allowed access to laboratory test reports and other subject records that are needed to verify the entries in the eCRF. The Investigators will allow the study monitor to inspect the various records of the study (eCRFs and other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements. These records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the Sponsor or designee, who is appointed to audit the study. Subject confidentiality will be maintained at all times.

The Investigators agree to cooperate with the study monitor to ensure that any problems detected in the course of the monitoring visits are resolved.

12.5 Retention of Study Documentation

The Investigator must retain study drug disposition records, copies of eCRFs and all study-related source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records will be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB/Ethics Committee). Notice of such transfer will be given in writing to the Sponsor or designee.

If the Investigator cannot guarantee this archiving requirement for any or all the documents at the investigational site, arrangements must be made between the Investigator and the Sponsor, to store these in a secure archive facility outside the site; they can therefore be returned to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside the site.

Following the study close-out visit data will be provided to the Investigator to store with the Investigator's study file for archiving purposes.

13 ACRONYMS AND DEFINITIONS

13.1 Acronyms

The acronyms listed below are a non-exhaustive list of those commonly used in Dermira study documents. Not all acronyms listed below are used within this document.

Abbreviation	Definition
AE	adverse event(s)
ALT	alanine amino-transferase
ANCOVA	analysis of covariance
AST	aspartate amino-transferase
BUN	blood urea nitrogen
C	celsius
CFR	code of federal regulations
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CRF	case report form
CRO	clinical research organization
CDLQI	Children's Dermatology Life Quality Index
eCRF	electronic case report form
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HCT	hematocrit
HDSS	hyperhidrosis disease severity scale
HGB	hemoglobin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IRB	institutional review board
IND	Investigational New Drug
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
IWRS	Interactive web response system
LOCF	last observation carried forward
LSR	local skin reaction
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities

Abbreviation	Definition
mmHg	millimeters of mercury
PI	Principal Investigator
RBC	red blood cells
SAE	serious adverse event(s)
SD	standard deviation
SSRI	serotonin reuptake inhibitors
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cells
WHO	World Health Organization
WOCBP	women of childbearing potential
β -hCG	beta human chorionic gonadotropin

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15 APPENDICES

Appendix A: Gravimetric Measurement of Sweat Production

Study sites must use the equipment and supplies provided by the Sponsor for the gravimetric procedure (Mettler balance, gauze pads, plastic bags, timer, non-latex, flock-lined gloves in multiple sizes and temperature/humidity device). A source document template will be provided to study sites to capture information on the gravimetric procedure.

The room used for the gravimetric procedure must be at a temperature of 68 to 76°F (20.0-24.0°C) and controlled for humidity. This information is recorded as part of the gravimetric procedure for each subject.

Prior to starting the gravimetric procedure, subjects must be evaluated for the appropriate size flock-lined glove and acclimated to the room where the procedure will be conducted. Flock-lined gloves will capture sweat production so the size selected should be snug but not overly tight.

Have all supplies ready in advance of starting the gravimetric procedure.

1. Clear the temperature device.
2. Place the subject in the room.
3. Record the start time of the acclimatization period, the room humidity and the room temperature at the beginning of the acclimation period.
4. Acclimation is 15 minutes in duration.
5. During acclimation, the subject should sit and may read or have study procedures performed.
6. Zero the Mettler balance.
7. Using gloved hands, place two 4x4 inch gauze pads and one flock-lined glove in a plastic bag. Compress bag to remove air and seal the bag. Record the weight of the gauze, non-latex glove and plastic bag.
8. Remove the plastic bag with the gauze and glove from the balance.
9. Remove the gauze and glove from the plastic bag.
10. Have the subject place the flock-lined glove on one hand.
11. The subject must keep the glove on for the 5-minute assessment period for sweat production.
12. Record start time and wait 5 minutes.
13. Record the stop time.
14. Lift the subject’s hand and slowly remove the glove. Press the gauze gently against both sides of the hand to fully absorb any residual sweat from the hand. Immediately place flock-lined glove and gauze back in the plastic bag.
15. Compress bag to remove air and seal the bag. Place the sealed plastic bag on the scale to record the weight of the gauze, flock-lined glove and plastic bag.

16. Zero balance.
17. Repeat the test as described above with the other hand.

Appendix B: Schedule of Events

Visit	Screening Period Day -21 to -1	Baseline Day 1	Day 4 Phone Call (+ 1 day)	Week 1 (+/-1 day)	Week 2 /Early Withdrawal (+/-1 day)
Informed Consent/Assent Form	X				
Demography	X				
Medical History	X	X			
Inclusion/Exclusion Criteria	X	X			
Physical Exam, Height, Weight	X				X[b]
Serum Chemistry and Hematology	X				X
Vital Signs	X	X		X	X
Adverse Events			X	X	X
Local Skin Reactions		X		X	X
Concomitant Medications	X	X		X	X
Urine Pregnancy Test	X	X			X
Hand Sweating Severity/ Daily Diary	X[a]	X		X	X
Hyperhidrosis Disease Severity Score		X		X	X
Gravimetric Measurement of Sweat		X		X	X
Dispense electronic diary	X				
Dispense Study Drug		X		X	
Study Drug Compliance				X	X

[a] Subjects will complete a minimum of 4-7 days within 7 days of randomization.
[b] Physical exam and weight only.

Appendix C: Hyperhidrosis Disease Severity Scale (HDSS)

Hyperhidrosis Disease Severity Scale	
Grade	**Definition**
1	My sweating is never noticeable and never interferes with my daily activities
2	My sweating is tolerable but sometimes interferes with my daily activities
3	My sweating is barely tolerable and frequently interferes with my daily activities
4	My sweating is intolerable and always interferes with my daily activities

Appendix D: Daily Diary (DD)

Please complete the following 3 questions in the diary each evening before you go to sleep.

Please be sure to think only about your hand sweating when answering these questions. The questions in this diary are designed to measure the severity and impact of any hand sweating you have experienced within the previous 24-hour period, including nighttime hours.

Item #1 (Subjects ≥16 years old)

During the past 24 hours, how would you rate your hand sweating **at its worst?**

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No sweating at all										Worst possible sweating

Item #2 (Subjects ≥16 years old)

During the past 24 hours, to what extent did your hand sweating impact your activities?

- ☐ Not at all
- ☐ A little bit
- ☐ A moderate amount
- ☐ A great deal
- ☐ An extreme amount

Item #3 (Subjects ≥16 years old)

During the past 24 hours, how bothered were you by your hand sweating?

- ☐ Not at all bothered
- ☐ A little bothered
- ☐ Moderately bothered
- ☐ Very bothered
- ☐ Extremely bothered

Item #4 (Completed at the end of treatment only)

Overall, how would you rate your hand sweating **now** as compared to before starting the study treatment?

1 = Much better

2 = Moderately better

3 = A little better

4 = No difference

5 = A little worse

6 = Moderately worse

7= Much worse

Appendix E: Hand Sweating Severity Children <16 years old

This question measures how bad your hand sweating was last night and today. Please think only about your hand sweating when answering this question. Please complete this question each night before you go to sleep.

Item #1-C

Thinking about last night and today, how **bad** was your hand sweating**?**

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No sweating at all										Worst possible sweating