CONFIDENTIAL

A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Topically Applied Sofpironium Bromide Gel, 15% in Subjects with Axillary Hyperhidrosis (the "Cardigan I Study")

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NAME OF INVESTIGATIONAL PRODUCT:	Sofpironium Bromide (BBI-4000)
ORIGINAL PROTOCOL	September 20, 2019
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Date: 2020.08.12 18:27:20 -04'00'

Deepak Chadha, MS, MBA, RAC
Chief Research and Development Officer

Date

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, Good Clinical Practice (GCP), and all applicable laws and regulations.

- Maintain all information supplied by Brickell Biotech, Inc. in confidence and, when this information is submitted to an Institutional Review Board (IRB) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

_____

Investigator Printed Name Signature Date

TABLE OF CONTENTS

SYNOPSIS

Protocol Title

A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Topically Applied Sofpironium Bromide Gel, 15% in Subjects with Axillary Hyperhidrosis (the "Cardigan I Study")

Study Objectives

- To evaluate the safety and local tolerability of sofpironium bromide gel, 15% when applied topically to subjects with primary axillary hyperhidrosis.
- To evaluate the effect of sofpironium bromide gel, 15% on hyperhidrosis disease severity as it relates to sweat production, patient-reported outcomes, and quality of life self-assessments.

Study Population

Subjects aged ≥9 years with a diagnosis of axillary hyperhidrosis.

Inclusion Criteria

Subjects must fulfill all the following criteria to be eligible for study admission:

1. Male or female subject ≥9 years of age in good general health.
2. Diagnosis of primary axillary hyperhidrosis in the opinion of the Investigator that meets all the following criteria:
    a. Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax 7-Item[1] [HDSM-Ax-7]) of 3 – 4 inclusive at both of the Screening Visits (Visits 1 and 4).
    b. Gravimetric test indicating a minimum of 50 mg of sweat production at rest in each axilla with a two-axilla combined total of at least 150 mg of sweat production in five (5) minutes at room temperature, 20°C to 25°C (68°F to 77°F), at Screening Visit 1 and at least one of Visits 2, 3, or 4.
    c. Symptoms of axillary hyperhidrosis for ≥6 months' duration.
3. The ability to understand and sign a written informed consent form (ICF), which must be obtained prior to any study-related procedures (including medication wash-out, if required) and treatment. Subjects less than the age of consent must sign an assent for the study, and a parent or a legal guardian must sign the informed consent form (if the subject reaches the age of consent during the study, they should be re-consented at the next study visit).
4. The ability to understand and sign a Health Insurance Portability and Accountability Act (HIPAA) authorization form, which shall permit the use and disclosure of the subject's individually identifiable health information.
5. The ability to understand and follow all study-related procedures including study drug administration.

[1] The HDSM-Ax-7 scale will be conducted using 7 of the 11 items in the HDSM-Ax scale. More specifically, the mean of the 2 items in Section 1 and the first 5 items in Section 2 (7 sub-items total) will be used. The mean will be derived by dividing the sum of the 7 item scores by 7. For each of the HDSM-Ax sub-items, missing values at EOT will be imputed. HDSM-Ax-7 at EOT will be derived from the imputed values.

6. Sexually active females of childbearing potential (FOCBP)* who are engaging in sexual activity that can cause pregnancy must agree to periodic pregnancy testing and use a medically acceptable method of contraception for the duration of the study. This includes perimenopausal women who are less than 12 months from their last menses. Acceptable contraceptive methods include the following:
    a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy); OR
    b. Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR
    c. Non-hormonal contraception, including intrauterine devices (≥1-week status post placement), or properly used barrier methods (e.g., male or female condoms with or without spermicide, cervical cap/diaphragm with spermicide).

    * FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Exclusion Criteria

The following criteria will exclude a subject from participating in this study:

1. In the Investigator's opinion, diagnosis of any skin or subcutaneous tissue conditions of the axilla(e), (i.e., the axillary area should be deemed otherwise "normal", besides the hyperhidrosis diagnosis, and free of blisters, large boils or sinus tracts, significant scarring, or open wounds).
2. Prior use of any prohibited medication(s) or procedure(s) for the treatment of axillary hyperhidrosis within the specified timeframe:
    a. Botulinum toxin to the axillary area within 9 months of GSP1 (Visit 2).
    b. Prior treatment with axillary iontophoresis within 4 weeks of GSP1 (Visit 2).
    c. Axillary thermolysis, sympathectomy, or any other treatment with a medical device or surgical procedure of the axillary area at any time in the past. Prior axillary laser hair removal is permitted if more than 28 days prior to GSP1 (Visit 2).
    d. Serotonergic agonist (or drugs that increase serotonin activity including selective serotonin re-uptake inhibitors [SSRIs]), beta-blocker, alpha-adrenergic agonist (clonidine), dopamine partial agonist, or tricyclic antidepressant treatment within 28 days of GSP1 (Visit 2). However, a subject who has been on a stable dose (in the opinion of the Principal Investigator) of any of these medications and has not had a recent change in hyperhidrosis frequency or severity for 3 months prior to the baseline visit may be included. Doses of these agents should not be altered during the course of the study.
    e. Any topical treatment for hyperhidrosis, requiring a prescription, within 28 days of GSP1 (Visit 2).
    f. Any over-the-counter topical antiperspirant/deodorant (applied directly to the axilla[e]) within 7 days of GSP1 (Visit 2). Non-antiperspirant deodorant will be provided by the Sponsor.
3. Anticholinergic agents used to treat conditions such as, but not limited to, hyperhidrosis, asthma, incontinence, gastrointestinal cramps, and muscular spasms by any route of administration (e.g., intravenous, oral, inhaled, topical, etc.) within 28 days of GSP1 (Visit 2).

4. All oral or topical homeopathic or herbal treatment (i.e., alternative therapies such as sage tablets, chamomile, valerian root, and St. John's wort) within 28 days of GSP1 (Visit 2).
5. Use of any cholinergic drug (e.g., bethanechol) within 28 days of GSP1 (Visit 2).
6. Use of any anti-anxiety and/or anti-depressant drugs, psychostimulants (e.g., amphetamine), or drugs with known anticholinergic side effects is prohibited with the following exceptions:
    a. A subject who has been on a stable dose of an anti-anxiety and/or anti-depressant drug and has not had a recent change in hyperhidrosis frequency or severity for ≥3 months may be included.
    b. Psychostimulants may be allowed if the dose has been stable for ≥3 months without change in hyperhidrosis frequency or severity.
    c. Drugs with known anticholinergic side effects (taken within the last 28 days), including dry mouth or blurred vision, may be allowed based on the Principal Investigator's assessment.

    NOTE: If anticholinergic side effect(s) are experienced on these medications prior to starting study medication, document the side effect(s) and severities in the source document and the electronic case report form. The doses of these agents should not be altered during the course of the study.
7. Known cause of hyperhidrosis or known history of a condition that may cause hyperhidrosis (i.e., hyperhidrosis secondary to any known cause such as hyperthyroidism, diabetes mellitus, medications, etc.).
8. Subjects with hyperhidrosis symptoms initiated or exacerbated with menopause.
9. Subjects with unstable type 1 or type 2 diabetes mellitus or thyroid disease, renal impairment, hepatic impairment, malignancy, glaucoma, intestinal obstructive or motility disease, obstructive uropathy, myasthenia gravis, benign prostatic hyperplasia (BPH), neurological conditions, psychiatric conditions, Sjögren's syndrome, sicca syndrome, or cardiac abnormalities that may alter normal sweat production or may be exacerbated by the use of anticholinergics in the Investigator's opinion.
10. Subjects with known hypersensitivity to glycopyrrolate, anticholinergics, or any of the components of the topical formulation.
11. Subject is pregnant, lactating, or is planning to become pregnant during the study.
12. Participating in a study or used an investigational drug or device within 28 days prior to GSP1 (Visit 2).
13. Any major illness within 28 days before the screening examination.
14. Any other condition including psychiatric illness (depression and/or anxiety) that would interfere with study participation and/or evaluation of study endpoints or laboratory abnormality that, in the opinion of the Investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
15. Employees of Brickell Biotech, Inc., the Investigator, or contract research organization (CRO) involved in the study, or an immediate family member (partner, offspring, parents, siblings, or sibling's offspring) of an employee involved in the study.

Study Design

Approximately 350 subjects, at up to approximately 45 clinical sites in the United States, will be randomized to receive either sofpironium bromide gel, 15% or vehicle gel (placebo) in a balanced 1:1 ratio in order to obtain approximately 300 evaluable subjects at the end of study.

Subjects will apply the investigational product (either sofpironium bromide gel, 15% or vehicle gel) once daily at bedtime to each axilla for 42 consecutive days.

Gravimetric measurements of sweat production and patient-reported outcomes HDSM-Ax-7 and Dermatology Life Quality Index (DLQI) (via electronic clinical outcomes assessment [eCOA] technology) will be recorded during the study at predefined time points. Patient Global Impression of Severity (PGI-S) will be administered with each administration of the HDSM-Ax, and the Patient Global Impression of Change (PGI-C) will be administered at the Day 43 visit (End of Treatment) only. Vital signs, local tolerability assessments, and adverse events will be collected at each visit. Blood and urine samples will be collected and analyzed at the Screening Visit and at the End of Treatment Visit for routine hematology, chemistry, and urinalysis parameters. Urine pregnancy testing for FOCBP will be performed at the Screening Visit, Baseline Visit, Visit 8 and End of Treatment.

A total of 13 scheduled visits will take place over approximately 11 to 15 weeks, depending on when the Baseline Visit (treatment) is scheduled after the three (3) screening period visits: initial screening, GSP1, and GSP2.

Test Product, Dose, and Mode of Administration

Either sofpironium bromide gel, 15%; or vehicle gel (placebo) topically applied to the axillae

Duration of Treatment

Forty-two days followed by a 14-day post-treatment follow-up visit

Safety Assessments

- Physical examination
- Vital signs
- Clinical laboratory assessments
- Urinalysis
- Collection of adverse events
- Subject-reported local tolerability assessments
- Investigator-reported local tolerability assessments

Efficacy Assessments

The following assessment measures will be conducted to evaluate the efficacy of sofpironium bromide gel:

- Hyperhidrosis Disease Severity Measurement-Axillary (HDSM-Ax-7) as measured by the subject (for subjects ≥12 years of age)
- Hyperhidrosis Disease Severity Measurement-Axillary, Child (HDSM-Ax-7, Child) as measured by the subject (for subjects ≥9 to <12 years of age)
- Gravimetrically measured sweat production (GSP)
- Dermatology Life Quality Index (DLQI) as measured by the subject (for subjects ≥17 years of age)
- Patient Global Impression Scales*; Severity (PGI-S**) and Change (PGI-C†)

* These questions will be included in the HDSM-Ax questionnaires
** Administered as Question #6 of HDSM-Ax at each assessment
† Administered as Question #7 of HDSM-Ax at the Day 43 visit only

Statistical Methods

Analysis Populations

Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all subjects who were randomized. Subjects will be analyzed according to the treatment group to which they were randomized, regardless of post randomization protocol deviations, including no treatment or wrong treatment received.

Per-Protocol Population

The Per-Protocol (PP) Population will be a subset of the ITT Population and will include subjects who meet the following criteria:

- Meets all inclusion/exclusion criteria
- Has not taken or applied any interfering concomitant medications
- Completed the following visits:
  - Visit 2 GSP 1, and the required GSP data collection
  - Visit 3 GSP 2, and the required GSP data collection
  - Visit 4 (Day 1) Re-screening/Baseline GSP 3 and HDSM-Ax, and the required GSP and HDSM-Ax data collection
  - Visit 10 (GSP 4) Day 41 (± 2 days), and the required GSP data collection
  - Visit 11 (GSP 5) Day 42 (± 2 days), and the required GSP data collection
  - Visit 12 (GSP 6) Day 43 (± 2 days) and HDSM-Ax, and the required GSP and HDSM-Ax data collection

Safety Population

The Safety Population will include all subjects randomized in the study who received study drug at least once. Subjects will be analyzed according to the treatment actually received. If a subject receives any sofpironium bromide gel, 15%, the subject will be analyzed in the sofpironium bromide gel group. Otherwise, the subject will be included in the vehicle group.

Efficacy

***Co-Primary Efficacy Endpoints*:**

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT).
- The change in GSP from baseline to EOT.

***Primary Efficacy Analyses*:**

The primary efficacy analysis will be performed on the ITT population. Both comparisons will be conducted using two-sided tests at an alpha=0.05 level. Both endpoints will need to demonstrate a statistically significant positive result in favor of the sofpironium bromide gel, 15% for the study to be considered successful.

The HDSM-Ax-7 co-primary endpoint will be analyzed using a logistic regression model with the following covariates: treatment, baseline HDSM-Ax-7 total score, and analysis center.

The GSP co-primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment, baseline ranked GSP, and analysis center. The ANCOVA may use rank-transformed or continuous data, pending the outcome of the Shapiro Wilk Normality test. The normality test will be performed prior to multiple imputation and separately for each arm. Should the normality assumption be violated for either arm, the primary analysis will use rank-transformed GSP data. If the normality assumption holds for both arms, the primary analysis will use continuous GSP data.

Methods for handling missing data for the Co-Primary Efficacy Endpoints

Before performing the primary analysis for the ITT population, missing EOT HDSM-Ax-7 and GSP values for the sofpironium bromide gel, 15% arm will be imputed for the co-primary efficacy endpoints by multiple imputations using a control-based imputation (CBI) model approach. Whereas, multiple imputations for missing values in the vehicle group will be performed assuming missing at random (MAR). For the GSP endpoint in particular, in order to ensure that the missing data imputation method is robust to outliers, data from subjects that meet the criterion for being an outlier will be removed from the imputation sampling database (i.e., the existing vehicle database).

Sensitivity Analyses of the Co-Primary Efficacy Endpoints

To further explore the robustness of the primary analysis results to different missing data assumptions, analyses using two more imputation methods will be performed: a missing data imputed to failure approach for the HDSM-Ax-7 co-primary endpoint, and a tipping point analysis for both the HDSM-AX-7 and GSP co-primary endpoints. Additionally, the ranked GSP and non-rank transformed GSP ANCOVA analyses will be repeated without imputing missing data, and again after removing outlier data. To further support the results of the co-primary endpoint HDSM-Ax-7, analysis of the 7 individual items in the scale will be conducted.

Secondary Efficacy Endpoints:

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to EOT.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT and achieving at least a 70% reduction in GSP from baseline to EOT.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to EOT and achieving at least a 50% reduction in GSP from baseline to EOT.

A gated, fixed-sequence testing procedure will be used to control the overall familywise error rate for the primary and secondary analyses. Testing will be performed first for the two co-primary endpoints. If both null hypotheses are rejected at the 2-sided 0.05 significance level in favor of sofpironium bromide gel, 15%, secondary efficacy endpoints will be tested in the order as specified above. Testing will continue only if all previously tested null hypotheses of no difference have been rejected at the 2-sided 0.05 significance level in favor of sofpironium bromide gel, 15%.

The secondary efficacy endpoints will be analyzed using methods similar to what is described for the co-primary endpoints.

Method of Pooling Sites to Generate Analysis Centers

Subjects from low enrolling sites will be pooled in order to generate analysis centers. The minimum number of subjects per analysis center is 10. The lowest enrolling site will be combined with the largest enrolling

site that does not meet the minimum requirement, and then the second lowest enrolling site and the second largest enrolling site will be combined, and so on. Further combining will be done until all analysis centers have at least 10 subjects. All analyses that are controlled for site will use this analysis center designation. Full details will be provided in the statistical analysis plan.

Psychometric Analysis of the HDSM-Ax-7-Item

In parallel to the traditional statistical analysis, psychometric evaluation of the HDSM-Ax-7-Item will be carried out to confirm the most appropriate HDSM-Ax-7-Item scoring algorithm and to examine internal validity, construct validity (i.e., examination of the magnitude of correlation between the HDSM-Ax total score and key variables such as items 4 and 5 of the HDSM-Ax-7-Item, PGI-S, PGI-C, and GSP), stability, reliability, ability to detect change, and interpretability of clinical trial results.

Safety

Safety analysis will be performed by treatment received for the Safety Population. Treatment-emergent adverse event (TEAE) descriptions will be mapped to standard terms, i.e., Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. At each post-baseline visit, the number and proportion of subjects reporting any given TEAE will be tabulated cumulatively by severity; each subject will be counted only once according to the worst severity reported up to the current visit. Separate tables will be constructed for (a) all reported TEAEs, (b) protocol treatment-related TEAEs, (c) serious TEAEs, (d) TEAEs leading to protocol treatment discontinuation, (e) protocol treatment-related serious TEAEs, (f) severe TEAEs, (g) TEAEs leading to dose interruption, (h) TEAEs of special interest, and (i) anticholinergic TEAEs.

At each visit, local tolerability assessments will be descriptively summarized by severity. An overall summary table will also be presented with subject incidences tabulated according to the worst severity experienced while on study. In addition, at each post-baseline visit, local tolerability will be summarized as cumulative shift tables versus baseline. Subject counts for each symptom will be cross-tabulated with baseline severity according to the maximum post-baseline severity reported for either axilla up to the current visit.

Laboratory parameters will be descriptively summarized (mean, standard deviation, median, minimum, maximum) for values obtained at Visit 1 and Visit 12. Whereas, vital signs will be summarized in a similar manner at each visit.

Sample Size and Power Estimation

Sample size estimation was performed for the co-primary efficacy endpoints based on the results of a Phase 2b study (BBI-4000-CL-203):

- HDSM-Ax-7 responder analysis: 2-point improvement response rates of 29.8% and 53.7% were assumed for the vehicle and sofpironium bromide gel, 15% arms, respectively. The power is 0.95 with 116 subjects per arm and a total of 232 subjects.
- GSP: using rank transformed GSP data for change from baseline to EOT, a difference of 16.6 in mean ranks between the vehicle and sofpironium bromide gel, 15% arms, with a pooled standard deviation of approximately 39.5, was used for this purpose. Normal approximation yielded a sample size estimate of 296 subjects for the study, 148 each arm, in order to achieve 0.95 power for the GSP co-primary endpoint.

A chi-square test for the HDSM-Ax-7 endpoint and a two-sample t-test for the GSP endpoint were used to estimate the above sample size and power for each endpoint. With approximately 300 evaluable subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP).

Additionally, sample size estimation was also performed using non-rank-transformed GSP data. An expected mean treatment difference of 73 mg with a pooled standard deviation of approximately 170 was used for this purpose. This yielded a reduced sample size estimate compared with the target of 300 subjects completing the co-primary efficacy assessments in order to achieve 0.95 power for GSP, further indicating that our sample size estimations are conservative.

Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment.

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BPH	Benign prostatic hyperplasia
CBI	Control-based imputation
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of Treatment
FDA	Food and Drug Administration
FOCBP	Female of childbearing potential
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GSP	Gravimetric sweat production
HDSM-Ax	Hyperhidrosis Disease Severity Measure-Axillary
HDSS	Hyperhidrosis Disease Severity Scale
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
I/E	Inclusion/exclusion
IEC	Institutional Ethics Committee
IRT	Interactive Response Technology
IND	Investigational New Drug Application

IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IV	Intravenous
LS	Least squares
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MNAR	Missing not at random
NF	National Formulary
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PT	Preferred term
RBC	Red blood cell
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SOC	System organ class
SSRI	Selective serotonin re-uptake inhibitor
TEAE	Treatment-emergent adverse event
UPT	Urine pregnancy test
US	United States
USP	United States Pharmacopeia
WBC	White blood cell

1 BACKGROUND AND CLINICAL RATIONALE

Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Primary hyperhidrosis (excessive sweating without an alternative origin) is localized, characteristically symmetric, and may involve several anatomic areas such as armpits, hands, and feet. It affects approximately 4.8% of the United States (US) population (Doolittle, 2016) and is believed to be caused by an overactive cholinergic response of the sweat glands. Current therapies have limited efficacy, significant side effects, and/or are invasive and costly.

Oral and topical anticholinergic drugs, such as glycopyrrolate, have been used to treat hyperhidrosis. The main limitations of these drugs are systemic anticholinergic side effects (e.g., blurred vision, dizziness, dry mouth, constipation, urinary retention, and tachycardia). Sofpironium bromide is a novel, soft-anticholinergic ester analog of glycopyrrolate and is in development for the topical treatment of axillary hyperhidrosis.

Sofpironium bromide is a competitive inhibitor of acetylcholine receptors located on certain peripheral tissues, including sweat glands. Sofpironium bromide gel is expected to inhibit the action of acetylcholine in sweat glands, thereby reducing the extent of sweating, and as a soft drug, is designed to provide maximal therapeutic effect with minimal side effects. Please refer to the sofpironium bromide gel Investigator's Brochure for more information.

In the current multicenter, randomized, double-blinded, vehicle-controlled, pivotal, Phase 3 study, Brickell is studying the safety, tolerability, and efficacy of topically applied sofpironium bromide gel, 15%, in subjects with primary axillary hyperhidrosis over a 6-week period, followed by a 2-week follow-up period.

Nonclinical Safety Conclusions

A comprehensive battery of pharmacology, safety pharmacology, absorption, distribution, metabolism, excretion (ADME), acute to chronic toxicity, genotoxicity, carcinogenicity (ongoing), and reproductive toxicity evaluations has been conducted to evaluate the safety of sofpironium bromide administration by the intended topical clinical route of administration.

Overall, the results of the nonclinical program support the safe use of sofpironium bromide gel at the intended maximum dosage for the treatment of primary axillary hyperhidrosis. Please refer to the sofpironium bromide gel Investigator's Brochure for additional information pertaining to the nonclinical studies.

Prior Human Experience

Brickell and its partner company (Kaken Pharmaceutical, Japan) have conducted multiple clinical studies of sofpironium bromide gel that encompass over 1300 subject exposures. These studies have evaluated the safety, tolerability, pharmacokinetics (PK), and efficacy of sofpironium bromide gel in adult and pediatric primary hyperhidrosis patients and healthy adult subjects. Please refer to the sofpironium bromide gel Investigator's Brochure for more detailed descriptions and results of the clinical studies.

Clinical Safety Conclusions

In studies conducted to date, three concentrations of sofpironium bromide gel, 5%, 10%, and 15%, demonstrated comparably acceptable safety and tolerability. Treatment-emergent adverse events (TEAEs) were mostly mild or moderate in severity with fewer subjects reporting TEAEs in the 5% gel group relative to the 10% and 15% gel groups. No deaths or drug-related serious adverse reactions have been reported in any sofpironium bromide gel clinical studies. Six serious adverse events have been reported and all were determined to be unrelated to

sofpironium bromide gel administration.

Consistent with the soft drug design, a low incidence of systemic anticholinergic adverse events (AEs) has been found in all clinical studies of sofpironium bromide gel. The most common anticholinergic AE was dry mouth, and all anticholinergic AEs were expected. Of note, the anticholinergic AEs were predominantly mild or moderate in severity and transient in duration (i.e., resolving gradually with continued use). All TEAEs completely resolved spontaneously with treatment discontinuation. Local application site tolerability reactions of burning, itching, pain, erythema, and dryness at the axillae were predominantly minimal in severity and typically transient.

Clinical Efficacy Conclusions

Overall, all three sofpironium bromide gel concentrations, 5%, 10%, and 15%, have exhibited a larger absolute mean reduction in gravimetric sweat production (GSP) from baseline to end of treatment (EOT) compared with vehicle. Better improvement in GSP response was associated with higher concentrations of sofpironium bromide. However, while there was a slight trend toward dose response, all gel concentrations were essentially equivalent in patient-reported outcome measures based on the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax), Dermatology Quality of Life Index (DLQI), and Hyperhidrosis Disease Severity Score (HDSS), suggesting that all three concentrations are efficacious. The response was seen as early as Day 8 and remained consistent throughout the applicable treatment period.

Clinical Pharmacokinetics Conclusions

In PK studies conducted to date, both sofpironium and its major metabolite BBI-4010 could be measured in the majority of subjects. Systemic exposure to sofpironium and BBI-4010 appeared to increase in an approximately dose-proportional manner when comparing the 5% and 15% gel concentrations, indicating that applying a more concentrated gel increased exposure. However, inter-subject variability of PK parameters was extremely high. Absorption is thought to be affected by skin thickness, temperature, hydration, and degree of occlusion.

Systemic exposure of sofpironium and BBI-4010 was typically minimal following the first dose (Day 1) and also after multiple doses (Day 21). Sofpironium accumulation after Day 1 was not observed. Plasma concentrations of BBI-4010 appeared to be lower than those of sofpironium. Steady state is likely reached within the first 24 hours. In general, plasma concentrations of sofpironium and BBI-4010 showed most samples analyzed were below 1 ng/mL, with many below the lower limit of quantification of 0.05 ng/mL for both sofpironium and BBI-4010.

Risk to Subjects

As an anticholinergic drug, administration of sofpironium bromide gel could be associated with signs or symptoms typical of anticholinergic effect such as dry mouth, blurred vision, dizziness, constipation, urinary retention, or tachycardia. The previous sofpironium bromide exposure to humans has demonstrated a low incidence of these effects, which are generally mild in severity. All such effects have been observed, and as expected, to be transient.

2 STUDY DESIGN

This is a multicenter, randomized, double-blinded, vehicle-controlled, Phase 3 study to evaluate the safety and efficacy of topically applied sofpironium bromide gel, 15% in subjects with primary axillary hyperhidrosis.

Approximately 350 subjects, at up to approximately 45 clinical sites in the US, will be enrolled to obtain approximately 300 evaluable subjects at the end of study.

Subjects will be randomized 1:1 to receive sofpironium bromide gel, 15% or vehicle gel (175 subjects dosed with 15% gel and 175 subjects dosed with vehicle gel). Subjects will apply the investigational product once daily at bedtime to their axillae for 42 consecutive days.

Patient-reported outcomes HDSM-Ax, Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C; EOT only), and DLQI, as well as Investigator-reported GSP, will be recorded during the study at predefined time points. Vital signs and local tolerability assessments will be collected at Visits 4 through 9 and Visits 12 (EOT) and 13. Adverse events will be collected at each post-Screening visit. Blood and urine samples will be collected and analyzed at Screening and Visit 12/EOT for routine hematology, chemistry, and urinalysis parameters. Additionally, a urine pregnancy test (UPT) for females of child-bearing potential (FOCBP) will be collected and analyzed at Visits 1, 4, 8, and 12.

A total of 13 scheduled visits will take place over approximately 11 to 15 weeks, depending on when the Baseline Visit (treatment) is scheduled after the three (3) screening period visits: initial screening, GSP1, and GSP2. See Section 7.1 for an events table of this study.

3 STUDY OBJECTIVES AND ASSESSMENTS

The purpose of this Phase 3 study is to assess the safety, local tolerability, and efficacy of sofpironium bromide gel, 15% when applied topically in subjects with primary axillary hyperhidrosis.

3.1 Study Objectives

- To evaluate the safety and local tolerability of sofpironium bromide gel, 15% when applied topically to subjects with primary axillary hyperhidrosis.
- To evaluate the effect of sofpironium bromide gel, 15% on hyperhidrosis disease severity as it relates to sweat production, patient-reported outcomes, and quality of life self-assessments.

3.2 Study Assessments

Safety Measures:

The following safety assessment measures will be conducted to evaluate the safety and local tolerability of sofpironium bromide gel, 15%:

- Physical examination
- Vital signs
- Clinical laboratory assessments
- Urinalysis
- Collection of AEs
- Subject-reported local tolerability assessments
- Investigator-reported local tolerability assessments

Efficacy Assessments:

The following assessment measures will be conducted to evaluate the efficacy of sofpironium bromide gel, 15%:

- HDSM-Ax 7-Item (HDSM-Ax-7) as measured by the subject (for subjects ≥12 years of age)
- Hyperhidrosis Disease Severity Measurement-Axillary, Child (HDSM-Ax-7, Child) as measured by the subject (for subjects ≥9 to <12 years of age)

- GSP
- DLQI as measured by the subject for subjects ≥17 years of age
- Patient Global Impression Scales* - Severity (PGI-S**) and Change (PGI-C†)

* These questions will be included in the HDSM-Ax questionnaires
** Administered as Question #6 of HDSM-Ax at each assessment
† Administered as Question #7 of HDSM-Ax at the Day 43 visit only

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 350 subjects, at up to approximately 45 clinical sites, will be randomized to receive either sofpironium bromide gel, 15% or vehicle gel in a 1:1 ratio to obtain approximately 300 evaluable subjects at the end of study.

4.2 Inclusion Criteria

Subjects must fulfill all of the following criteria to be eligible for study admission:

1. Male or female subject ≥9 years of age in good general health.
2. Diagnosis of primary axillary hyperhidrosis in the opinion of the Investigator that meets all the following criteria:
    a. HDSM-Ax-7[2] of 3-4 inclusive at both of the Screening visits (Visits 1 and 4)
    b. Gravimetric test indicating a minimum of 50 mg of sweat production at rest in each axilla with a two-axilla combined total of at least 150 mg of sweat production in five (5) minutes at room temperature, 20°C to 25°C (68°F to 77°F), at Screening Visit 1 and at least one of Visits 2, 3, or 4
    c. Symptoms of axillary hyperhidrosis for ≥6 months' duration
3. The ability to understand and sign a written informed consent form (ICF), which must be obtained prior to any study-related procedures (including medication wash-out, if required) and treatment. Subjects less than the age of consent must sign an assent for the study, and a parent or a legal guardian must sign the informed consent form (if the subject reaches the age of consent during the study, they should be re-consented at the next study visit).
4. The ability to understand and sign a Health Insurance Portability and Accountability Act (HIPAA) authorization form, which shall permit the use and disclosure of the subject's individually identifiable health information.
5. The ability to understand and follow all study-related procedures including study drug administration.
6. Sexually active females of childbearing potential (FOCBP)* who are engaging in sexual activity that can cause pregnancy must agree to periodic pregnancy testing and use a medically acceptable method of

[2] The HDSM-Ax-7 scale will be conducted using 7 of the 11 items in the HDSM-Ax scale. More specifically, the mean of the 2 items in Section 1 and the first 5 items in Section 2 (7 sub-items total) will be used. The mean will be derived by dividing the sum of the 7 item scores by 7. For each of the HDSM-Ax sub-items, missing values at EOT will be imputed. HDSM-Ax-7 at EOT will be derived from the imputed values.

contraception for the duration of the study. This includes perimenopausal women who are less than 12 months from their last menses. Acceptable contraceptive methods include the following:

a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy); OR
b. Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR
c. Non-hormonal contraception, including intrauterine devices (IUD; ≥1 week status post placement), or properly used barrier methods (e.g., male or female condoms with or without spermicide, cervical cap/diaphragm with spermicide).

* FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

4.3 Exclusion Criteria

Meeting any of the following criteria will exclude a subject from participating in this study:

1. In the Investigator's opinion, diagnosis of any skin or subcutaneous tissue conditions of the axilla(e), (i.e., the axillary area should be deemed otherwise "normal", besides the hyperhidrosis diagnosis, and free of blisters, boils or sinus tracts, significant scarring, or open wounds).
2. Prior use of any prohibited medication(s) or procedure(s) for the treatment of axillary hyperhidrosis within the specified timeframe:
   a. Botulinum toxin to the axillary area within 9 months of GSP1 (Visit 2).
   b. Prior treatment with axillary iontophoresis within 4 weeks of GSP1 (Visit 2)
   c. Axillary thermolysis, sympathectomy, or any other treatment with a medical device or surgical procedure of the axillary area at any time in the past. Prior axillary laser hair removal is permitted if more than 28 days prior to GSP1 (Visit 2).
   d. Serotonergic agonist (or drugs that increase serotonin activity including selective serotonin re-uptake inhibitors [SSRIs]), beta-blocker, alpha-adrenergic agonist (clonidine), dopamine partial agonist, or tricyclic antidepressant treatment within 28 days of GSP1 (Visit 2). However, a subject who has been on a stable dose (in the opinion of the Principal Investigator) of any of these medications and has not had a recent change in hyperhidrosis frequency or severity for 3 months prior to the baseline visit may be included. Doses of these agents should not be altered during the course of the study.
   e. Any topical treatment for hyperhidrosis, requiring a prescription, within 28 days of GSP1 (Visit 2).
   f. Any over-the-counter topical antiperspirant/deodorant (applied directly to the axilla[e]) within 7 days of GSP1 (Visit 2). Non-antiperspirant deodorant will be provided by the Sponsor.
3. Anticholinergic agents used to treat conditions such as, but not limited to, hyperhidrosis, asthma, incontinence, gastrointestinal cramps, and muscular spasms by any route of administration (e.g., intravenous [IV], oral, inhaled, topical, etc.) within 28 days of GSP1 (Visit 2).
4. All oral or topical homeopathic or herbal treatment (i.e., alternative therapies such as sage tablets, chamomile, valerian root, and St. John's wort) within 28 days of GSP1 (Visit 2).

5. Use of any cholinergic drug (e.g., bethanechol) within 28 days of GSP1 (Visit 2).
6. Use of any anti-anxiety and/or antidepressant drugs, psychostimulants (e.g., amphetamine), or drugs with known anticholinergic side effects is prohibited with the following exceptions:
    a. A subject who has been on a stable dose of an anti-anxiety and/or antidepressant drug and has not had a recent change in hyperhidrosis frequency or severity for ≥3 months may be included.
    b. Psychostimulants may be allowed if the dose has been stable for ≥3 months without change in hyperhidrosis frequency or severity.
    c. Drugs with known anticholinergic side effects (taken within the last 28 days) including dry mouth or blurred vision may be allowed based on the Investigator's assessment.

    NOTE: If anticholinergic side effect(s) are experienced on these medications prior to starting study medication, document the side effect(s) and severities in the source document and the electronic case report form (eCRF). The doses of these agents should not be altered during the course of the study.
7. Known cause of hyperhidrosis or known history of a condition that may cause hyperhidrosis (i.e., hyperhidrosis secondary to any known cause such as hyperthyroidism, diabetes mellitus, medications, etc.).
8. Subjects with hyperhidrosis symptoms initiated or exacerbated with menopause.
9. Subjects with unstable type 1 or type 2 diabetes mellitus or thyroid disease, renal impairment, hepatic impairment, malignancy, glaucoma, intestinal obstructive or motility disease, obstructive uropathy, myasthenia gravis, benign prostatic hyperplasia (BPH), neurological conditions, psychiatric conditions, Sjögren's syndrome, sicca syndrome, or cardiac abnormalities that may alter normal sweat production or may be exacerbated by the use of anticholinergics in the Investigator's opinion.
10. Subjects with known hypersensitivity to glycopyrrolate, anticholinergics, or any of the components of the topical formulation.
11. Subject is pregnant, lactating, or is planning to become pregnant during the study.
12. Participating in a study or used an investigational drug or device within 28 days prior to GSP1 (Visit 2).
13. Any major illness within 28 days before the screening examination.
14. Any other condition, including psychiatric illness (depression and/or anxiety) that would interfere with study participation and/or evaluation of study endpoints or laboratory abnormality that, in the opinion of the Investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
15. Employees of Brickell Biotech, Inc., the Investigator, or contract research organization (CRO) involved in the study, or an immediate family member (partner, offspring, parents, siblings, or sibling's offspring) of an employee involved in the study.

5 INVESTIGATIONAL PRODUCT (IP)

Sofpironium bromide gel is an anhydrous gel formulation containing the drug substance in a gel base comprising hydroxypropyl cellulose National Formulary (NF), hexylene glycol NF, isopropyl myristate NF, citric acid anhydrous United States Pharmacopeia (USP), and alcohol dehydrated USP. Sofpironium bromide gel is a clear

to slightly translucent colorless gel and is packaged in a white-colored, metered pump container. One pump container is packaged in a carton with 2 applicators. The total gel volume in each pump container is ~50 mL (~43 g). The gross weight of each full container at baseline is approximately 78 to 84 grams.

Based on one full pump actuation delivering ~0.67 mL of the gel formulation, a total of approximately 38 mL of gel is required for 4 weeks (28 days) of daily dosing to the axillae. Therefore, each pump container is sufficient for ≥28 days of dosing per protocol instructions. A new container will be dispensed to each subject at Baseline (Visit 4) and Day 22 (Visit 7).

5.1 Storage of Investigational Product

The investigational product must be stored in a secure area with access limited to the Investigator and authorized site staff and administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in this protocol.

Investigational product should be stored at controlled room temperature 68ºF to 77ºF (20ºC to 25ºC) with brief excursions permitted between 59°F to 86°F (15ºC to 30ºC). Maintenance of a temperature log (manual or automated) is required.

5.2 Instructions for Use and Administration of Investigational Product

Investigational product kit cartons will be provided to each site and will include one individual plastic pump container per each carton. Each carton will also contain 2 applicators. An investigational plastic pump container will contain sufficient drug product for a 28-day treatment period.

Each carton will have a unique identifier number printed on the label. The pump container label will display the same unique identifier number.

Each subject will be randomized via an Interactive Response Technology (IRT) system to receive either sofpironium bromide gel, 15%, or vehicle gel (placebo) to topically apply, once daily at bedtime, to each axilla using the supplied applicators for 42 consecutive days. Instructions on the use of the IRT system will be provided in a separate manual.

Subjects will be instructed to apply the investigational gel product to each axilla using all the gel expressed from **one full actuation** of the pump per each axilla dose application. Each full actuation of the pump corresponds to approximately 86.5 mg of sofpironium bromide in the 15% investigational product.

The subject will apply all doses of investigational product at night, prior to going to bed, using the supplied applicators. Subjects will apply their first dose of gel prior to bedtime on the night of their Baseline Visit. The subject will be instructed to continue applying the investigational product each night with the last application to occur the night before attending the end of treatment evaluation (i.e., Visit 12). Subjects should wash the applicator each night after dosing. Two applicators are provided in each kit to compensate for loss or damage during handling; it is not necessary to use all the applicators over the specified dosing interval.

To ensure accurate dosing, the study staff will be instructed to first prime and then weigh each pump container before dispensing to the subject. Priming is accomplished by fully pressing the pump for five (5) sequential actuations; the dispensed gel from these 5 priming actuations is considered waste and should be discarded.

The weight of the pump container, with the cap on, will be recorded for the uniquely numbered container after priming and can then be dispensed to the subject. Over the course of the study, a container will be primed, weighed, and dispensed at both the Baseline Visit (Visit 4, Day 1) and Visit 7 (Day 22) for a total of 2 containers

dispensed. Each of the 2 containers previously dispensed will be returned by the subject at a next respective visit (Visit 7 and Visit 12 [EOT]), weighed with the cap on, and weight recorded per the unique bottle number. At the End of Treatment visit (Visit 12), the subject will bring the 2nd container to his/her visit for the final weight determination; however, no additional investigational product will be dispensed. Study subjects may return the applicators, or they may discard them after dosing is completed.

At each visit, gel application instructions and compliance will be discussed and documented.

5.3 Instructions for the Subjects

Subjects will be instructed to apply the investigational product every day, at night prior to bedtime, using a supplied applicator as follows (a written instruction sheet and access to a study product application video and digital mobile application will be supplied to the subject):

1. Expose the underarm areas and ensure they are dry. Do not wash the underarm areas for at least 30 minutes prior to application.
2. Hold the plastic applicator between the index and middle fingers and the thumb of the left hand. Carefully, by applying consistent pressure to the actuator with an index finger, dispense the gel of ONE FULL actuation onto the dome of the white plastic applicator.
3. Immediately apply study product to the right underarm area.
4. Distribute all the gel expressed using the plastic applicator in a way that covers all the underarm area where the hair grows by gently applying a layer of the product.
5. Repeat the procedure to apply the study product to the left underarm using the right hand.
6. Thoroughly wash both hands and rinse the plastic applicator.
7. Allow the study product to dry for 5 minutes before putting any clothes on the upper body.

Important information:

- The subject should sleep in a T-shirt or similar pajama to avoid touching the underarm area while sleeping.
- Subjects should maintain their underarm grooming habits as follows:
    - Do not shower, shave, or wash the underarm area for at least 8 hours AFTER study product application.
    - Shaving of the underarm area should be done at least 8 hours BEFORE study product application.
    - If the subject takes a shower or washes the underarm area at night then it should be at least 30 minutes before study product application.
    - Subjects should ensure the underarm areas are dry prior to application of the study product.
- Subjects should not apply any other product to the axillary area (including the supplied non-antiperspirant deodorant) for at least 8 hours after study product application.
- The subject should use the applicator provided to avoid contact with skin of the hands. Special care should be taken to avoid contact of the gel with the eyes or mouth. Of note, hands should be washed after applying the gel to avoid possible skin and eye contact with the gel.

- The study product contains alcohol and is flammable. The subject should avoid fire, flames, or smoking during the application and until the gel has dried. The subject should not expose the container to fire, flames, or extreme heat.

On the day of a clinic study visit:

- Showering and shaving in the morning is permissible.
- Do not apply any product to the axilla (including Sponsor-supplied non-antiperspirant deodorant).
- Exercise is to be avoided (e.g., gym, jogging, etc.).
- Avoid caffeine and tea until the gravimetric assessments are completed.

5.4 Procedures for Blinding and Unblinding

This is a double-blind study. All study treatments (sofpironium bromide gel, 15%, and vehicle gel) are identical in color, shape, size, and packaging in order to maintain the blind.

Subjects, Sponsor personnel, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at central laboratories will remain blinded to the identity of the treatment from the time of randomization until database lock and unblinding, using the following methods: (1) randomization data will be maintained by a third party, kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study; (2) the identity of the treatments will be concealed by the use of study treatments that are identical in packaging, labeling, schedule of administration, and appearance.

The treatment assignments for all enrolled subjects will be unblinded only after the conclusion of the study. Specifically, the blind will be broken only after all data are verified, entered into the database, and validated; subject evaluability assessments are performed and entered into the database; and the database is locked. In the case of a medical emergency, the Investigator can break the blind for the subject involved preferably by first discussing the situation with the medical monitor and the Sponsor (or designee) immediately. After confirmation, the Investigator will be contacted with unblinding information by a Sponsor representative. The Investigator will record the code break in the subject's source documents.

6 CONCOMITANT MEDICATIONS/TREATMENTS

Information will be recorded on concomitant medications/treatments (e.g., aspirin, Tylenol, birth control pills, intrauterine device [IUD], vitamins) taken during study participation, or which may require a washout for study participation. Every effort should be made to keep dosing with any concomitant medications consistent/constant during the study.

6.1 Permissible Medications/Treatments

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. If the permissibility of a specific medication/treatment is in question, the Medical Monitor should be contacted.

Subjects will be instructed to not apply any contraindicated topical product to their axillary area (see list in Section 6.2). The Sponsor-supplied non-antiperspirant deodorant should not be applied within 8 hours following the application of study product (suggest applying in the morning).

6.2 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment is made with the safety of the study participant as the primary consideration. When possible, Brickell Biotech's Medical Monitor should be notified before a prohibited medication/treatment is administered.

Prior to the inclusion of a subject in the study, as specified in Sections 4.2 and 4.3 (inclusion/exclusion criteria), and throughout the duration of the study, the use of the following medications/treatments is prohibited:

- Anticholinergic agents used to treat conditions such as, but not limited to, hyperhidrosis, asthma, incontinence, gastrointestinal cramps, and muscular spasms by any route of administration (e.g., IV, oral, inhaled, topical including topical glycopyrrolate or derivatives).
- Any oral or topical homeopathic or herbal treatment (i.e., alternative therapies such as sage tablets, chamomile, valerian root, and St. John's wort).
- Any prescription topical products, including topical prescription antiperspirants or similar agents (e.g., Drysol, Xerac AC, Certain DRI) and hand sanitizers applied to the axillae for the duration of the study.
- Any treatment or procedure for axillary hyperhidrosis including but not limited to:
    - botulinum toxin
    - thermolysis treatments including microwave (e.g., MiraDry), laser, or other(s)
    - sympathectomy
    - iontophoresis
- Any surgical procedure involving the axillae (including laser hair removal), or any surgical procedures that will result in significant scarring of the axillae.
- Any oral cholinergic (e.g., bethanechol) throughout the duration of the study.
- **Addition of, or change of dose** for any medication that is allowed as specified in Sections 4.2 and 4.3 (inclusion/exclusion criteria) including the following:
    - serotonergic agonists (or drugs that increase serotonin activity including SSRIs)
    - beta-blockers
    - alpha-adrenergic agonists (clonidine)
    - dopamine partial agonists
    - tricyclic antidepressants
    - anti-anxiety and/or other anti-depressant drugs
    - amphetamine products
    - drugs with known anticholinergic side effects.

7 PROCEDURES

The timing of each assessment is listed in the Time and Events Table (Section 7.1).

Each subject will report for 13 distinct visits (over 11-15 weeks).

All Screening assessment results must be completed and reviewed prior to the GSP1 Visit (within 31 days). Therefore, none of the Screening Visit days can occur on the same day as the Baseline Visit.

Subjects may be consented for up to 31 days before the GSP1 Visit. Subjects outside this screening window shall be re-consented and certain screening activities may need to be repeated. Prior to enrollment into the treatment

phase of the study, the Investigator or designee will contact the Medical Monitor to address such subjects on a case-by-case basis.

In the event of restrictions due to COVID-19, or any other pandemic, the Sponsor may, with IRB approval where required, during the study implement some or all study assessments and procedures associated with patient visits to be conducted remotely or by home visits (per FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020) when the patients' ability to visit investigator sites is impacted.

7.1 Time and Events Table

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
PROCEDURE	Screening			Rescreening / Baseline								End of Treatment	Follow-up
Gravimetric Timepoint		GSP 1[1]	GSP 2[1]	GSP 3[1]						GSP 4	GSP 5	GSP 6	
Day (allowable window)	*Up to 31 days prior to GSP1*			*(Day 1)*	Day 8 (± 2)	Day 15 (± 2)	Day 22 (± 2)	Day 29 (± 2)	Day 36 (± 2)	Day 41 (±2)	Day 42 (± 2)	Day 43 (± 2)	Day 57 (± 3)
Informed Consent/Assent	X												
Medical History, Demographics	X			X									
Physical Exam				X									
Vital Signs (blood pressure, heart rate, respiratory rate, and temperature)				X	X	X	X	X	X			X	X
I/E Criteria	X			X									
Gravimetric Assessments[2,3]	X	X	X	X	X	X	X	X	X	X	X	X	X
HDSM-Ax[4,5]	X			X	X	X	X	X	X	X	X	X	X
DLQI[6]				X		X						X	
Local Tolerability Assessments[7]				X	X	X	X	X	X			X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Randomization[8]				X									
Non-antiperspirant Deodorant Dispensed[9]	X												
Investigational Product[10] (IP) Dispensed / Returned				X			X					X	
IP Weight[11]				X			X					X	
Compliance Evaluation					X	X	X	X	X	X	X	X	
Safety Labs (hematology, chemistry, and urinalysis)	X											X	
UPT (females of childbearing potential only)[12]	X			X				X				X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Optional End of Study Patient Survey[13]													X

Abbreviations: DLQI = Dermatology Life Quality Index; FOCBP = females of child-bearing potential; HDSM-Ax = Hyperhidrosis Disease Severity Measure-Axillae; I/E = inclusion/exclusion; IP = investigational product; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; UPT = urine pregnancy test

[1] Visit 2 should occur no more than 31 days after the initial screening visit (Visit 1); both Visits 2 and 3 should occur within 14 days of rescreening/baseline Visit 4. Visit 4 will correspond to Day 1.

[2] Gravimetric assessments for all visits will be conducted from **7:00am-11:00am**.

[3] One 5-minute gravimetric assessment will be conducted for each axilla.

[4] PGI-S will be administered as Question #6 of HDSM-Ax at every assessment; PGI-C will be administered as Question #7 of HDSM-Ax at the Day 43 visit only.

[5] Version of HDSM-Ax questionnaire to be administered according to subject age (≥9 to <12 years or ≥12 years of age).

[6] The DLQI will be administered to subjects ≥ 17 years of age.

[7] Investigator assessments to be performed after the Subject assessments.

[8] Randomization will take place only after the subject is qualified at the Rescreening Visit (Visit 4).

[9] Non-antiperspirant deodorant will be dispensed at the Screening Visit (Visit 1) and resupplied as needed throughout the study.

[10] Pump container 1 of 2 to be primed, weighed, and dispensed to subject at Baseline (Visit 4). Pump 2 of 2 to be primed, weighed, and dispensed to subject at Day 22 (Visit 7). Written instructions for nightly dosing will be given to the subject. Subjects will apply their first dose of gel prior to bedtime the night of their Baseline visit. Instruct the subjects to return Pump container 1 of 2 at Day 22 (Visit 7) and Pump container 2 of 2 at Day 43 (Visit 12, End of Treatment).

[11] Pump container 1 of 2 will be weighed with the applicator cap on after priming at Baseline prior to dispensing to the subject and upon return at Day 22 (Visit 7). Pump container 2 of 2 will be weighed with the applicator cap on after priming at Day 22 (Visit 7) prior to dispensing to the subject and upon return at Day 43 (Visit 12, End of Treatment).

[12] FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

[13] Optional end of study survey will be offered to subjects ≥ 17 years of age.

7.2 Visit-Specific Procedures

7.2.1 Visit 1: Screening (Days -31 to 0)

Written informed consent must be obtained prior to any study-related procedures. Potential subjects will be screened within 45 days prior to Visit 4 (Rescreening/Baseline) to assess their eligibility to enter the study. Only eligible subjects with axillary hyperhidrosis will be enrolled.

After informed consent is obtained, the following procedures will be performed:

- Collect and review subject medical history and demographics.
- Assess inclusion/exclusion criteria.
- Subject to complete the GSP assessment.
    - GSP assessments for all visits will be conducted from **7:00 am to 11:00 am**.
    - One 5-minute GSP assessment will be conducted for each axilla.
    - Refer to Appendix 1 for instructions and requirements of sample collection and handling.
- Subject to complete the HDSM-Ax assessment.
    - Five multi-part questions and PGI-S question (administered as Question #6 at the end of the HDSM-Ax questionnaire) to be completed by the subject prior to other assessments.
    - Refer to Appendix 2 (HDSM-Ax) and Appendix 3 (HDSM-Ax Child)
- Perform UPT if applicable (FOCBP only). If positive, the subject shall be screen failed.
- Collect samples for laboratory assessments (hematology, chemistry, and urinalysis) (see Section 8.1.3).
- Review concomitant medications/treatments and assess for washouts.
- Provide subject with the Sponsor-provided non-antiperspirant deodorant. Resupply as needed throughout subject study participation.
- Schedule the subject to return for Visit 2 (GSP1) after any washout has been completed; must be within 31 days of Visit 1 (Screening).

In the event a subject does not satisfy the sweat production eligibility (Inclusion criterion 2b) at the Screening Visit but is otherwise eligible to continue (i.e., satisfies all other eligibility requirements including HDSM-Ax severity but may still require a washout), the Screening GSP may be retested once during the screening period at the discretion of the Investigator:

- Retest must occur within the 31 days from Screening (Visit 1) and must occur prior to GSP1 (Visit 2).
- HDSM-Ax must also be completed at the time of the Screening GSP retest.
- If subject does not meet inclusion based on GSP and HDSM-Ax results at the time of the retest, the subject shall be screen failed and may not be rescreened.

The subject shall be reminded that, on the day of each clinic study visit:

- Showering in the morning is permissible.
- Do not apply any product to the axilla (including Sponsor-supplied deodorant).
- Exercise is to be avoided (e.g., gym, jogging, etc.).
- Avoid caffeine and tea until the gravimetric assessments are completed.

7.2.2 Visits 2 and 3: GSP1 and GSP2

Visit 2 should occur no more than 31 days after the initial screening visit (Visit 1); both Visits 2 and 3 should occur within 14 days of Rescreening/Baseline Visit 4. Any washouts required for prohibited medications (see Section 4.3) must be completed prior to Visit 2 (GSP1).

The following activities will be conducted:

- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Review the subject's health (AEs).
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.3 Visit 4: GSP3 (Day 1; Rescreening/Baseline) +14 Days of Visit 2

No more than 14 days may elapse between Visit 2 (GSP1) and Visit 4 (GSP3; Day 1).

The following activities will be conducted:

- Collect and review subject medical history and demographics.
- Perform physical examination including collection of height and weight (see Section 8.1.1).
- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature) after subject has been seated for ≥2 minutes.
- Assess inclusion/exclusion criteria.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete the HDSM-Ax assessment.
    - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Subjects ≥ 17 years of age to complete the DLQI questionnaire.
    - 10 questions to be completed by the subject.
    - Refer to Appendix 4.
- Perform local tolerability assessments (see Section 8.1.5).
- Review changes to the subject's health (AEs).
- Perform urine pregnancy testing (UPT) if applicable (FOCBP only). If positive, the subject shall be excluded from the study.
- Provided the subject has passed all inclusion/exclusion criteria, randomize the subject according to separate instructions.
- Pull from inventory the pump container whose unique identifier matches that assigned by the IRT system at randomization. Record the unique IP gel pump container number on the source document. Dispense study product container 1 (of 2) to the subject as follows:
    - Write subject number and initials on the study product container label.
    - Prime the pump (5 actuations) and discard expressed gel.
    - Weigh the primed pump with the applicator cap on and record in source prior to dispensing to the subject. Dispense the pump to the subject in the kit carton with the included 2 applicators.
    - Provide subject with subject study drug application brochure, access to a study product application video and digital mobile application.
    - Review with subject the study drug application procedure (refer to Appendix 6).

- Instruct subject to apply the first application of study medication at home the evening of Visit 4 (Baseline visit).
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.4 Visit 5: Day 8 ± 2 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature) after subject has been seated for ≥2 minutes (see Section 8.1.2).
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am.**
- Subject to complete HDSM-Ax assessment.
  - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Evaluate subject compliance:
  - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
  - Verbally confirm application process.
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.5 Visit 6: Day 15 ± 2 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
  - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Subject to complete the DLQI questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Evaluate subject compliance:
  - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
  - Verbally confirm application process.
- Review concomitant medications/treatments.
- Remind subject to bring their study medication to next visit.
- Schedule the subject to return for the next study visit.

7.2.6 Visit 7: Day 22 ± 2 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
  - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Evaluate subject compliance:
  - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
  - Verbally confirm application process.
- Collect subject's previously dispensed study product container, weigh with the applicator cap on, and record weight of container.
- Dispense study product container (2 of 2).
  - Access the IRT system to obtain the number of the next assigned pump container to dispense. Pull from inventory the pump container whose unique identifier matches that assigned by the IRT system. Record the unique IP gel pump container number on the source document.
  - Write subject number and initials on the study product container label.
  - Prime the pump (5 actuations) and discard expressed gel.
  - Weigh the primed pump with the applicator cap on and record in source prior to dispensing to the subject.
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.7 Visit 8: Day 29 ± 2 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
  - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Evaluate subject compliance:
  - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
  - Verbally confirm application process.

- Perform UPT if applicable (FOCBP only). If positive, the subject shall be withdrawn from the study.
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.8 Visit 9: Day 36 ± 2 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
    - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Evaluate subject compliance:
    - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
    - Verbally confirm application process.
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.9 Visits 10 and 11: GSP4 (Day 41) ± 2 Days and GSP 5 (Day 42) ± 2 Days

Visits 10 and **11** will occur as separate visits on Days 41 and 42.

The following activities will be conducted:

- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
    - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Review changes to the subject's health (AEs).
- Evaluate subject compliance:
    - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
    - Verbally confirm application process.
- Review concomitant medications/treatments.
- At Visit 11, remind subject to bring their study medication to next visit.
- Schedule the subject to return for the next study visit.

7.2.10 Visit 12: GSP6 (Day 43; End of Treatment) ± 2 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
  - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
  - Subject to complete PGI-C administered as Question #7 at the end of the HDSM-Ax questionnaire.
- Subject to complete the DLQI questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Collect subject's previously dispensed study product container, weigh with the applicator cap on, and record weight of container.
- Evaluate subject compliance:
  - Ask subjects whether they applied the study product to the right and left axilla each evening as directed and confirm reason for any missed doses.
  - Verbally confirm application process.
- Collect samples for laboratory assessments (hematology, chemistry, and urinalysis).
- Perform UPT if applicable (FOCBP only). If positive, the subject shall be withdrawn from the study.
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.11 Visit 13: Follow-up (Day 57) ± 3 Days

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the GSP assessment; will be conducted from **7:00 am to 11:00 am**.
- Subject to complete HDSM-Ax assessment.
  - Subject to complete PGI-S administered as Question #6 at the end of the HDSM-Ax questionnaire.
- Subjects ≥ 17 years of age to complete optional End of Study Survey.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Review concomitant medications/treatments.
- Discharge subject from the study.

7.3 Unscheduled Visits

If a subject is seen for an unscheduled visit, an assessment and record of AEs should be completed, as appropriate. Additional evaluations should be performed as necessary, and the appropriate CRF pages should be completed.

7.4 Early Discontinuation of Subjects

It is the right and duty of the Investigator to discontinue a subject's participation if the subject's health or wellbeing is threatened by continuation in the study. In the event of premature discontinuation, the Investigator should determine the primary reason for discontinuation. A subject may be discontinued from the study if any of the following circumstances occur:

- The subject experiences a SAE rendering him or her unable to continue study participation.
- The subject experiences an AE that in the opinion of the Investigator may pose a significant risk for continued participation of the subject in the study.
- The subject is unable to physically or mentally tolerate the use of the investigational product.
- An exclusion criterion becomes apparent at any time during the study; the Medical Monitor must be contacted to discuss prior to discontinuing subject participation.
- The subject is not compliant with the study procedures; the Medical Monitor must be contacted to discuss prior to discontinuing subject participation.
- The subject voluntarily withdraws from the study. When possible, attempt to identify the reason the subject withdrew consent and document with particular attention paid to whether an underlying AE is at cause.
- The subject becomes pregnant.
- If for any reason per the Investigator's or the Sponsor's judgment, discontinuation is in the subject's best interest.

Subjects who discontinue the study prior to the completion of all treatment visits will be asked to complete the evaluations corresponding to Visit 12 (Day 43, End of Treatment). The Sponsor will be notified of early discontinuation as soon as possible during the study.

8 RESPONSE MEASURES AND SUMMARY OF DATA COLLECTION METHODS

8.1 Safety Measures

The following safety assessment measures will be conducted as indicated in Section 7.1, Time and Events Table.

- Physical examination
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Laboratory tests (hematology, chemistry, urinalysis) and pregnancy testing in FOCBP
- Collection of AEs
- Local tolerability assessments

8.1.1 Physical Examination

Physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. Height and weight will also be measured and recorded.

8.1.2 Vital Signs

Subjects should be seated for ≥2 minutes prior to measurements. Pulse rate (bpm) will be counted over 60 seconds. Blood pressure (mmHg) will be measured with a sphygmomanometer.

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

8.1.3 Clinical Laboratory Assessments

Hematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed below:

Hematology

Platelet count	*RBC Indices*:	*Automated WBC Differential*:
Red blood cell (RBC) count	Mean corpuscular volume (MCV)	Neutrophils
White blood cell (WBC) count	Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

Blood urea nitrogen	Chloride	Alkaline phosphatase
Creatinine	Aspartate aminotransferase (AST)	Total and direct bilirubin
Sodium	Alanine aminotransferase (ALT)	
Potassium	Gamma glutamyl transferase (GGT)	

Routine Urinalysis

Bilirubin, color, appearance, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen
Microscopic examination (if blood or protein is abnormal)

Other Screening Tests

Urine Pregnancy Test (females of childbearing potential* only, using UPT tests provided by the Sponsor.)
* Females of childbearing potential for this study includes any female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

All results will be reported and must be reviewed by the Investigator or designee. Abnormal results shall be assessed for clinical significance. Repeat laboratory testing may be requested at the discretion of the Investigator. If an AE should require laboratory testing, the results of the test should be obtained by the investigative site and filed in the subject's documentation.

8.1.4 Adverse Events

Adverse events (AEs; see Section 9.2) will be collected for all untoward medical occurrences in a subject entered into this clinical study (e.g., signed consent), whether or not a pharmaceutical product has been administered. Any event, including local tolerability assessments (see Section 8.1.5), that requires specific treatment, results in interruption of treatment, or results in discontinuation of the subject from the study will also be reported as an AE.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

8.1.5 Local Tolerability Assessments

Local tolerability assessments (see Appendix 5) will be evaluated through assessment of symptoms at the drug application site. These assessments are to be performed for both axillae individually. Subject assessments will be made prior to the Investigator assessments.

Subject Local Tolerability Assessments: Subjects will be queried about whether any symptoms occurred at the study drug application site within the previous 24 hours and further whether any such symptoms persisted longer than 1 hour following study drug application. Standardized scales will be used to describe specifically the severity of any burning, stinging, or itching.

Investigator Local Tolerability Assessments: Investigators will observe for the existence of any significant local symptoms at the study drug application site. Significant local symptoms are defined as those not ordinarily observed following application of a topical product. Standardized scales will be used to describe specifically the severity of any erythema or scaling.

Local tolerability signs and symptoms that result in a subject requiring a concomitant therapy, interruption of treatment, or discontinuation from the study, will be reported as AEs.

8.1.6 Subject Assessments

Subjects must complete ALL self-assessments while at the clinic (i.e., HDSM-Ax, DLQI, PGI-S, PGI-C) prior to assessments being made by the Investigator. Please see Appendix 2 and Appendix 3 (HDSM-Ax by age; also includes PGI-S and PGI-C) and Appendix 4 (DLQI) for a full description of these assessments. Subjects will also have the option to complete an End of Study Survey. The HDSM-Ax, DLQI, PGI-S, and PGI-C assessments, as well as the optional End of Study Survey, will be collected electronically using a tablet device. Site personnel will be trained and a separate electronic clinical outcomes assessment (eCOA) manual will be supplied.

8.2 Summary of Methods of Data Collection

This protocol will utilize validated 21 Code of Federal Regulations (CFR) Part 11 compliant electronic data capture (EDC) software and eCOA software to collect required study data. The Investigator must ensure that data are properly recorded on each subject's eCRFs, eCOAs, and related documents. When changes or corrections are made in the eCRF, the EDC systems will maintain an audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals listed on the Delegation of Responsibilities Log with responsibility for eCRF completion may make entries in the eCRFs.

The Investigator or physician Sub-Investigator must electronically sign and date each subject's eCRF for each timepoint completed. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

8.3 Efficacy Measures

The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 15% as indicated in the Procedures Section 7.1:

- HDSM-Ax as measured by the subject
- GSP as measured by the Investigator
- DLQI as measured by the subject (for subjects ≥17 years of age)
- Patient Global Impression Scales; Severity (PGI-S) and Change (PGI-C)

9 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

9.1 Safety Evaluations

The Investigator is responsible for the appropriate medical care and the safety of subjects who have entered this study. The Investigator must document any AE experienced by subjects who have entered this study and report all SAEs to the CRO (see Section 9.3.1). Contact information for the Sponsor's Medical Monitor is provided on the protocol cover page.

9.2 Adverse Events

9.2.1 Definitions of Adverse Events

According to 21 CFR Parts 312.32 and 320.32 (IND Safety Reporting, Applicability of Requirements Regarding an "Investigational New Drug Application"), Food and Drug Administration (FDA) Guidance for Industry (Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans) (Federal Register/Vol. 75, No. 188/September 29, 2010) and International Council on Harmonisation (ICH) E2A (Clinical Safety and Data Management: Definitions and Standards for Expedited Reporting):

An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE.

The following information should be considered when determining whether or not to classify a test result, medical condition, or other incident as an AE:

Adverse events will be recorded from the time of informed consent.

Abnormal laboratory values should not generally be recorded as AEs unless an intervention is required, the laboratory abnormality results in an SAE, the lab abnormality results in study termination or interruption/discontinuation of study treatment, or the lab abnormality is associated with clinical signs or symptoms. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Complications that occur in association with a protocol-mandated intervention (e.g., invasive procedures such as biopsies) should be recorded as AEs.

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis under a single event term. For example, cough, rhinitis, and sneezing might be grouped together as "upper respiratory tract infection." If possible, abnormal laboratory results that meet the definition of an AE (see above) should be reported as a clinical diagnosis rather than the abnormal value itself (e.g., "anemia" rather than "decreased blood count").

9.2.1.1 Documentation and Monitoring Adverse Events

All AEs encountered during the clinical trial following subject consent through the last study drug visit will be recorded on the appropriate Adverse Events eCRF.

Special considerations:

Elective procedures or routinely scheduled treatments are not considered AEs. However, an untoward medical event occurring in association with a prescheduled elective procedure should be recorded as an AE.

A baseline condition is not considered an AE unless the condition worsens following study drug administration.

Death itself is not considered an AE; it is, instead, the outcome of an AE.

SAEs that are considered related (i.e., determined to be possibly, probably, or definitely related) to sofpironium bromide by the Investigator or Sponsor should be followed until the event resolves or stabilizes (see Section 9.4).

9.2.1.2 Assessment of Adverse Events

For each AE, the start and resolution dates, intensity, seriousness (i.e., whether the event meets the definition of an SAE [Section 9.3.1]), relationship of the event to the study drug, action taken regarding study drug, and outcome of the event will be documented on the eCRF.

Intensity

The following definitions should be used to assess and grade AE intensity, including laboratory abnormalities judged to be clinically significant.

Severity	Grade	Description
Mild	**1**	Awareness of sign or symptom, but easily tolerated
Moderate	**2**	Discomfort enough to cause interference with usual activity

Severity	Grade	Description
Severe	**3**	Incapacitating with inability to work or do usual activity

Note: a severe adverse event is not necessarily serious.

Relationship

The relationship of an AE to study drug should be assessed using the guidelines presented in the table below. An AE for which there has been no causal relationship reported will require follow-up to determine causality.

Adverse Event Relationships to Study Drug

Degree of Certainty	Description
Definitely Related	An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).
Probably Related	An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.
Possibly Related	An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.
Unlikely Related	An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.
Not related	An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

Outcome

Each AE will be characterized according to the outcomes described in the following table:

Outcome	Description
Recovered/Resolved	The subject has fully recovered from the event with no observable residual effects.
Recovering/Resolving	The effects of the event are improving, or events have stabilized (are constant and not expected to improve or worsen) but have not returned to baseline.
Not recovered/Not Resolved	The effects of the event are still present and changing. The event is not considered stabilized or resolved.
Recovered/Resolved with Sequelae	The subject has fully recovered from the event with some observable residual effects.
Fatal	The event was the primary cause of death (may or may not be the immediate cause of death).
Unknown	The event outcome is unknown.

Death is an outcome of an event and not an event *per se*. Sudden death or death due to unexplainable cause(s) is to be reported, but follow-up will be pursued until cause of death is determined.

Action Taken with Study Drug

Action taken with study drug in relation to each adverse event will be characterized as follows:

- None
- Drug withdrawn
- Drug interrupted
- Dose reduction
- Unknown
- Not applicable
- Other (specify on eCRF)

9.3 Serious Adverse Events

Any AE that is serious (see definition below) and occurs after administration of study drug must be reported to the CRO Medical Monitor within 24 hours of discovery of the event. An event occurring after informed consent but before administration of study drug that is considered serious and possibly related to a protocol procedure must also be reported to the CRO within 24 hours of discovery of the event.

9.3.1 Definition and Reporting Procedures

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	The adverse event resulted in death.
Life Threatening:	The adverse event placed the subject at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.

Fatal:	The adverse event resulted in death.
Hospitalization:	The adverse event required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not serious adverse events by this criterion. Hospitalizations or prolonged hospitalizations for scheduled therapy need not be captured as SAEs.
Disabling/Incapacitating:	Resulted in a substantial and permanent disruption of the subject's ability to carry out activities of daily living.
Congenital Anomaly or Birth Defect:	An adverse outcome in a child or fetus of a subject exposed to the study drug or study treatment regimen before conception or during pregnancy.
Medically Significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

Every SAE (regardless of suspected causality) should be reported to the CRO Medical Monitor within 24 hours of discovery of the event. The processes for reporting and documenting SAEs are provided in the study manual. Investigators are responsible for reporting these events to their Institutional Review Board/Institutional Ethics Committee (IRB/IEC) in accordance with federal and institutional laws and regulations.

Additional updates from the Investigator may be necessary as more information becomes available on the SAE, and all treatment-related SAEs will be followed until the acute event has resolved or stabilized, even if the subject discontinues study participation prior to the SAE resolution. Any new information or follow-up information pertaining to previously reported SAEs will be reported to the CRO Medical Monitor within 24 hours of becoming aware of the new or follow-up information. The new or follow-up information should be faxed to 919-313-1412 (US toll-free: 1-866-761-1274) or e-mailed to safety-inbox.biotech@iqvia.com.

Any SAE that occurs after study completion, and is considered by the Investigator to be related to sofpironium bromide, should be reported to the Sponsor.

Reporting Serious Adverse Events to Regulatory Agencies

The Sponsor will determine which SAEs qualify for expedited reporting to regulatory agencies. SAEs that qualify for expedited reporting will be submitted to regulatory agencies in accordance with federal regulation (21 CFR 312.32).

9.4 Follow-up of Adverse Events and Laboratory Test Abnormalities

AE information will be collected during the clinical trial from the time the subject signs informed consent through the final study visit. SAEs that are considered related to study drug by the Investigator or Sponsor should be followed until the events resolve or stabilize.

9.5 Pregnancy Reporting

Sexually active females of childbearing potential (FOCBP)* must have a negative pregnancy test prior to study enrollment and must use an acceptable method of contraception during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

FOCBP must agree to periodic pregnancy testing and use a medically acceptable method of contraception for the duration of the study. This includes perimenopausal women who are <12 months from their last menses. Acceptable contraceptive methods include the following:

- Abstinence for the duration of the study or where partner is sterile (e.g., vasectomy); OR
- Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR
- Non-hormonal contraception, including IUD (≥1-week status post placement) or properly used barrier methods (e.g., male or female condoms with or without spermicide, cervical cap/diaphragm with spermicide).

***** FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Subjects who become sexually active or begin to have relations with a partner who is not sterile during the trial must agree to use an acceptable form of birth control for the duration of the study.

9.5.1 Time Period for Collecting Pregnancy Information

FOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or Investigator suspects that a subject may be pregnant at any time during the study, the investigational product must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further investigational product and must be discontinued from the study.

9.5.2 Action to Be Taken If Pregnancy Occurs

If following initiation of investigational product, it is subsequently discovered that a trial subject was pregnant or may have been pregnant at the time of investigational product exposure, the Investigator must immediately notify the CRO Medical Monitor of this event, and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to the CRO Medical Monitor by fax to 919-313-1412 (US toll-free: 1-866-761-1274) or e-mailed to safety-inbox.biotech@iqvia.com. The Investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the Investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the Investigator must report to the CRO Medical Monitor, on the appropriate pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal (period immediately before and after birth) and neonatal (infants up to 28 days after birth) outcome.

Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs (or SAEs, if they fulfill the SAE criteria). **Offspring will be followed for a minimum of eight weeks.** Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) will be recorded as a SAE and details documented in the pregnancy surveillance form. An abortion, whether accidental, therapeutic, elective or spontaneous, will be reported as a SAE.

9.6 Other Safety Measures

Safety will also be assessed by physical examinations, laboratory tests, and measurement of vital signs assessed as indicated throughout the study schedule. Clinically significant changes in these parameters may be captured as adverse events.

10 STATISTICAL PROCEDURES

A detailed statistical analysis plan (SAP) will be generated prior to the final database lock. Database lock will follow completion of data entry, verification and validation, database audit, and data clarification resolution.

10.1 Analysis Populations

The three analysis populations for this study are defined below. Identification of the subjects to be included in each analysis population will be determined and finalized prior to database unmasking.

10.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all subjects who were randomized. Subjects will be analyzed according to the treatment group to which they were randomized, regardless of post-randomization protocol deviations, including no treatment or wrong treatment received.

10.1.2 Per-Protocol Population

The PP Population will be a subset of the ITT Population and will include subjects who meet the following criteria:

- Meets all inclusion/exclusion criteria
- Has not taken or applied any interfering concomitant medications
- Completed the following visits:
    - Visit 2 GSP 1, and the required GSP data collection
    - Visit 3 GSP 2, and the required GSP data collection
    - Visit 4 (Day 1) Re-screening/Baseline GSP 3 and HDSM-Ax, and the required GSP and HDSM-Ax data collection
    - Visit 10 (GSP 4) Day 41 (± 2 days), and the required GSP data collection
    - Visit 11 (GSP 5) Day 42 (± 2 days), and the required GSP data collection
    - Visit 12 (GSP 6) Day 43 (± 2 days) and HDSM-Ax, and the required GSP and HDSM-Ax data collection

10.1.3 Safety Population

The Safety Population will include all subjects randomized in the study who received study drug, either vehicle or sofpironium bromide gel, 15%, at least once. If a subject received any sofpironium bromide gel, 15%, the subject will be analyzed in the sofpironium bromide gel, 15%, treatment group. Otherwise the subject will be included in the vehicle group.

10.2 Efficacy Endpoints

10.2.1 Definitions

For the purposes of analysis, Baseline and End of Treatment (EOT) definitions for the two primary efficacy assessment measures, HDSM-Ax-7 and Gravimetric Sweat Production (GSP), are defined below.

HDSM-Ax

- Baseline = Visit 4 (Day 1) assessment
- EOT = Visit 12 (Day 43) assessment

GSP

- Baseline = the median of GSP1, GSP2, and GSP3 measurements obtained on Visit 2, Visit 3, and Visit 4, respectively
- EOT = the median of GSP4, GSP5, and GSP6 measurements obtained on Visit 10, Visit 11, and Visit 12, respectively

Note that at each timepoint, GSP will be defined as the sum of both axillae measurements. If 1 axilla value is missing at a timepoint, then the non-missing observed value will be multiplied by 2. The values for baseline or EOT will not be regarded as missing as long as the measurement is available at least for one of the three timepoints.

10.2.2 Co-Primary Efficacy Endpoints

The following co-primary efficacy endpoints will be analyzed to assess the efficacy of sofpironium bromide gel, 15%:

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT.
- The change in GSP from baseline to EOT.

Note that the assessment of the first co-primary efficacy endpoint will be conducted using 7 of the 11 items on the HDSM-Ax scale. More specifically, the mean of the 2 items in section 1 and the first 5 items in section 2 (7 sub-items in total) will be used. The mean will be derived by taking the sum of 7 item scores and dividing it by 7. For each of the HDSM-Ax sub-items, missing values at EOT will be imputed as described briefly in Section 10.3.1. HDSM-Ax-7 at EOT will be derived from the imputed values. Further details on imputation methods will be provided in the SAP.

10.2.3 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed:

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to EOT.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT and achieving at least a 70% reduction in GSP from baseline to EOT.

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to EOT and achieving at least a 50% reduction in GSP from baseline to EOT.

10.2.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints to be analyzed include the following:

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax 11-Item (HDSM-Ax-11) scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-11 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax Question 4 score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax Question 4 score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax Question 5 score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax Question 5 score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, (EOT), and 57.
- Change in PGI-S from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- PGI-C score on Day 43 (EOT).
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-11 scale score from baseline to EOT and achieving at least a 70% reduction in GSP from baseline to EOT.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-11 scale score from baseline to EOT and achieving at least a 50% reduction in GSP from baseline to EOT.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score and achieving at least a 70% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-11 scale score and achieving at least a 70% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score and achieving at least a 50% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-11 scale score and achieving at least a 50% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.

- Change in HDSM-Ax-7 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57 as a continuous measure.
- Change in HDSM-Ax-11 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57 as a continuous measure.
- The proportion of subjects achieving at least a 70% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 50% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The rank-based GSP change from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The absolute GSP change from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The percent change from baseline in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The change in the modified DLQI from baseline to Day 15 and Day 43 (EOT).

10.3 Analysis Methods

The primary efficacy analysis will be performed on the ITT population with missing values imputed. The co-primary efficacy endpoints are:

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT in the sofpironium bromide gel, 15% group versus vehicle; and
- The change in GSP from baseline to EOT in the sofpironium bromide gel, 15% group versus vehicle.

Both comparisons will be conducted using two-sided tests at an alpha=0.05 level. Both endpoints will need to demonstrate a statistically significant positive result in favor of sofpironium bromide gel, 15% for the study to be considered successful.

The key elements of the primary efficacy analysis for each co-primary endpoint are described below.

10.3.1 Primary and Secondary Analysis of the HDSM-Ax-7 Co-Primary Endpoint

Data: HDSM-Ax-7 total scores 2-point responder status (0, 1) at EOT. Missing data will be imputed first before analysis is performed.

Imputation Model: Imputation will be item-level. If a subject is missing values for any of items 1a, 1b, 2a, 2b, 2c, 2d, or 2e at Visit 4 (Day 1), the Visit 1 (Screening) value will be used as Baseline. If the Visit 1 (Screening) value is also missing, the subject will be excluded from all HDSM-Ax-7 change from baseline analyses. If a subject is missing Day 43 value, the closest (in time) available non-missing value from Day 41 (±2 days) or Day 42 (±2 days) will be used as the first level of imputation. Should none of the Days 41, 42, and 43 values be available, multiple imputations of missing EOT item-level scores will be performed on the sofpironium bromide gel, 15% arm values using a control-based imputations (CBI) methodology (see Section 10.3.4). Multiple imputations assuming missing at random will be performed for missing data for vehicle subjects. The HDSM-Ax-7 score will be calculated using the imputed item-level values. Further details on imputation methods will be provided in the SAP.

Analysis Model: Logistic Regression Model

Covariates: The following covariates are planned:

- Treatment (class effect: sofpironium bromide gel, 15% group, vehicle group)
- Baseline HDSM-Ax-7 total score
- Analysis center (see Section 10.3.3)

Hypothesis Tested:

The null hypothesis:

> H_0: The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT is the same in the sofpironium bromide gel, 15%, and vehicle arms

will be tested against the two-sided alternative hypothesis:

> H_1: The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to EOT is not the same in the sofpironium bromide gel, 15%, and vehicle arms.

Estimand: The estimand of this co-primary efficacy analysis is the difference in proportions between sofpironium bromide gel, 15%, and vehicle arms with a 2-point improvement from baseline to EOT in HDSM-Ax-7 total scores among all ITT subjects, regardless of treatment adherence.

As a secondary, supportive analysis, change from baseline to EOT will be analyzed as a continuous measure. The analysis model will be an ANCOVA model with treatment, baseline HDSM-Ax-7 score, and analysis center as covariates. The estimand for this analysis is the difference in mean baseline to EOT changes in HDSM-Ax-7 total scores between sofpironium bromide gel, 15%, and vehicle arms among all ITT subjects, regardless of treatment adherence.

In addition, a separate site poolability analysis will be performed with analysis center-by-treatment interaction terms added to the primary analysis model. An overall $p < 0.10$ for the combined interaction terms will be regarded as an indication of potential heterogeneity among the analysis centers. A mixed model analysis will then be performed with analysis center as a random effect to account for the potential heterogeneity.

10.3.2 Primary and Secondary Analyses of the GSP Co-Primary Endpoint

Data: Either rank-based GSP change from baseline to EOT or continuous GSP change from baseline to EOT will be analyzed. The GSP assessment is known to be a highly variable measure, and as such, the Shapiro Wilk test of normality will be performed to determine if the co-primary endpoint will be continuous or rank transformed. The normality test will be performed prior to multiple imputation for missing data and separately for each arm. Should the normality assumption be violated for either arm, the co-primary endpoint will be analyzed using rank-transformed GSP data. If the normality assumption holds for both arms, then the co-primary endpoint will be analyzed using continuous GSP data.

For the rank transformation of GSP measurements at a particular time point, continuous data for all subjects will be ranked together without regard to treatment assignment, from smallest to highest value. The smallest observation will be assigned the rank of 1, the second smallest the rank of 2, and so on. Average ranks will be used for tied observations. For determination of baseline value for a subject, the continuous GSP data will be ranked separately at each of Visits 2, 3, and 4; the median of the three ranks will be used as baseline value of the subject. Using the measurement data from Visits 10, 11, and 12, the rank-transformed GSP value at EOT will be derived in the same manner. For each subject, the difference between the rank-transformed baseline and EOT GSP values (EOT – baseline) will serve as the outcome value for the rank-based GSP ANCOVA analysis.

Missing EOT GSP data (continuous data) will be imputed before analysis is performed.

Imputation Model: Imputation will be done using continuous data prior to rank-transformation, should the normality assumption be violated. For continuous data, subjects with results (see Section 10.3.3) meeting the criterion for "outlier" will be removed from imputation sampling database (i.e., data for vehicle patients) prior to missing data imputation. From the remaining imputation sampling database of continuous GSP measurements, multiple imputations of missing EOT sofpironium bromide, 15% arm GSP values will be performed using a CBI methodology (see Section 10.3.4). Multiple imputations assuming MAR will be performed for missing EOT data Vehicle subjects. Further details on multiple imputations will be provided in the SAP.

Analysis Model: ANCOVA model (either non-ranked or ranked, pending outcome of normality test)

Fixed effects: The following fixed effects are planned:

- Treatment (class effect: sofpironium bromide gel, 15% group, vehicle group)
- Baseline GSP (either non-ranked or ranked, pending outcome of normality test)
- Analysis center (see Section 10.3.3)

Hypothesis Tested:

The null hypothesis:

> H_0: The rank-based GSP changes from baseline to EOT are the same in the sofpironium bromide gel, 15%, and vehicle groups

will be tested against the two-sided alternative hypothesis:

> H_1: The rank-based GSP changes from baseline to EOT are not the same in the sofpironium bromide gel, 15%, and vehicle groups.

Estimand: The estimand of this co-primary efficacy analysis is the mean difference between treatments, sofpironium bromide gel, 15%, versus vehicle, in the change from baseline to EOT for GSP among all ITT subjects, regardless of treatment adherence.

Additionally, the following secondary and supportive analyses will be performed for the GSP co-primary endpoint:

(a) Using the same methodology as described above, an ANCOVA analysis will be performed for either the non-rank transformed, continuous GSP data, or the rank transformed GSP data, pending the results of the normality test. If the normality assumption is violated and the rank-transformed data are used as the co-primary endpoint, analysis of the continuous data will be supportive. If the normality assumption holds and the continuous data are used as the co-primary endpoint, then analysis of the rank-transformed data will be supportive.

(b) To further address the potential large variations in GSP data, mixed model repeated measures (MMRM) analyses will be performed to estimate the average sofpironium bromide gel, 15% treatment effect over the 6-week course of treatment, i.e. the average sofpironium bromide gel, 15% versus vehicle difference from baseline to Days 8, 15, 22, 29, 36, and EOT, using both rank-based and non-rank-based data. As the MMRM methodology is known to be robust to missing data, missing data will not be imputed for this analysis. In addition, based on the BBI-4000 CL-203 results, treatment versus visit interactions are not expected. Details of the analysis models will be provided in the SAP.

(c) For the primary endpoint of either ranked or continuous GSP (pending normality test results), a separate site poolability analysis will be performed with analysis center-by-treatment interaction terms added to the primary analysis model. An overall $p < 0.10$ for the combined interaction terms will be regarded as an indication of

potential heterogeneity among the analysis centers. A mixed model analysis will then be performed with analysis center as a random effect to account for the potential heterogeneity.

10.3.3 Method of Pooling Sites to Generate Analysis Centers

Subjects from low enrolling sites will be pooled in order to generate analysis centers. The minimum number of subjects per analysis center is 10. For sites with <10 enrollments, the lowest enrolling site will be combined with the largest enrolling site, and then the second lowest enrolling site and the second largest enrolling site will be combined, and so on. Further combining will be done as necessary until all analysis centers have at least 10 subjects. All analyses that are controlled for site will use this analysis center designation. Site poolability will also be assessed as described in Sections 10.3.1 and 10.3.2. Full details will be provided in the SAP.

10.3.4 Handling of Missing Data for the Co-Primary Efficacy Endpoints in the ITT Population

For both HDSM-Ax-7 and GSP, multiple imputations for missing values in the vehicle group will be performed assuming MAR. For the sofpironium bromide gel, 15% group, multiple imputations using the CBI model will be employed as the primary imputation method to handle missing data. This approach will adopt a missing not at random (MNAR) assumption and missing values in the sofpironium bromide gel, 15%, group will be imputed based on a distribution with estimated values at visits lost to follow-up similar to that of subjects in the vehicle group. This approach further assumes that for the treatment effect observed in sofpironium bromide gel, 15% arm, subjects with missing data gradually trends towards the estimated mean in the vehicle group, i.e., any treatment benefit gained is not immediately lost upon withdrawal. The same co-primary analysis models will be applied to the multiple imputed datasets and the results combined via Rubin's rules (Rubin, 1976).

Furthermore, in order to ensure that the missing data imputation method proposed is robust to outliers for the GSP co-primary endpoint, data from subjects that meet the criterion for being an outlier will be removed from the imputation sampling database as follows. Combining the vehicle and sofpironium bromide gel, 15% arms, the mean and standard deviation will be calculated for the non-missing GSP change from baseline to EOT data. Data values more than 3 standard deviations away from the mean will be regarded as outliers. However, since the outliers are included in the original mean and standard deviation calculations and would have inflated their values, the outliers will be set aside and the mean and standard deviation will be re-calculated to see if any additional outliers are identified. This process will be repeated until no more outliers are identified. Prior to performing imputation for missing GSP change from baseline data in the ITT population, data values contributing to the outlying observations will be removed from the imputation sampling database, i.e. the non-missing vehicle data. With this approach, outlying data will not be propagated during missing data imputation. Once an imputation is complete, all original non-missing data and the imputed, previously missing data will be used for the GSP ITT analysis. Further details for this approach will be included in the SAP.

10.3.5 Sensitivity Analyses of the Co-Primary Efficacy Endpoints

To further explore the robustness of the primary analysis results to different missing data assumptions, analyses using two additional imputation methods will be performed as presented below. Furthermore, the ranked GSP and non-rank transformed GSP ANCOVA analyses will be repeated without imputing missing data, and again after removing outlier data. Additionally, the 7 items in the HDSM-Ax-7 scale will be analyzed individually to support the primary analysis for this co-primary endpoint.

Summary of Sensitivity Analyses of the Co-Primary Efficacy Endpoints

	Co-Primary Efficacy Endpoint Assessed	Sensitivity Analysis
1	GSP change from baseline to EOT	Analysis performed on available data only without imputing missing data; using both ranked and non-ranked data.
2	GSP change from baseline to EOT	Subjects with outlying data removed from analysis; using both ranked and non-ranked data (multiple imputations for missing data).
3	HDSM-Ax-7 2-point improvement from baseline to EOT	Missing data imputed as failure/non-response (single imputation only)
4	HDSM-Ax-7 2-point improvement and GSP change from baseline to EOT	Tipping point analysis (multiple imputations for missing data)
5	HDSM-Ax-7 2-point improvement from baseline to EOT	Analysis of the 7 individual items in the HDSM-Ax-7 scale (multiple imputations for missing data)

Unless otherwise specified, sensitivity analyses pertain to the primary analyses for the co-primary endpoints only. A brief description of each sensitivity analysis is provided below; complete details will be included in the final SAP.

Sensitivity Analysis 1: To further investigate the robustness of the GSP co-primary efficacy endpoint, the ranked and non-rank transformed GSP analyses will be repeated on all available data only without imputing missing data. The methodology will be similar to the primary analysis of the GSP co-primary endpoint.

Sensitivity Analysis 2: To further investigate the robustness of the GSP co-primary efficacy outcome, the ranked and non-rank transformed GSP analyses will be repeated after removing outlier data (as defined in Section 10.3.4). The methodology will be similar to the primary analysis of the GSP co-primary endpoint, except that outlier data will be removed from the imputed database for these analyses.

Sensitivity Analysis 3: Missing post-baseline HDSM-Ax-7 data will be imputed as failure/non-response in both treatment groups. The co-primary efficacy HDSM-Ax-7 analysis will be re-run on the so-imputed HDSM-Ax-7 dataset and treatment success proportion estimates will be produced.

Sensitivity Analysis 4: A tipping point analysis will be conducted to investigate the robustness of the co-primary efficacy outcomes. Tipping point analyses will be conducted separately for the HDSM-Ax-7 and GSP co-primary endpoints.

For the GSP co-primary endpoint, missing data in the vehicle arm will be assumed to be MAR, while missing data from the sofpironium bromide gel, 15%, arm will be imputed assuming that subjects with missing data have missing GSP data that are worse by a prespecified Δ compared to similar subjects with observed data. Missing values will be multiply imputed via this method with increasing Δ values. A Δ increment of 5 mg will be used for this study. The GSP co-primary efficacy outcome analysis methodology will be applied to the imputed datasets and repeated until statistical significance no longer holds. The tipping point will be identified and the results will be summarized graphically.

For the HDSM-Ax-7 co-primary endpoint, identical imputation methodology to that described above for the GSP will be applied to the HDSM-Ax-7 total scores, and the resulting values will be dichotomized into responders

versus non-responders using the 2-point improvement criterion. A Δ increment of 0.5 (on a 0-4 scale) will be used for this study. The HDSM-Ax-7 co-primary efficacy outcome analysis methodology will be applied to the imputed datasets and repeated until statistical significance no longer holds. The tipping point will be identified and the results will be summarized graphically.

Sensitivity Analysis 5: A sensitivity analysis will be conducted to investigate whether any of the individual items in the HDSM-Ax-7 scale are overly influencing changes observed in the total score. First, a subject will be counted as a responder if they achieve at least a 2-point improvement in the individual question from baseline to EOT. The logistic regression model for the primary analysis for HDSM-Ax-7 will be repeated for each of the 7 individual items, and each individual question will be analyzed separately. Secondly, one of the 7 items will be omitted, and the HDSM-Ax-7 total score will be calculated as the average of the remaining 6 items. The primary logistic regression analysis for 2-point improvement response rate will be performed on this 6-item scale. This process will be repeated 7 times, each time with a different item of the HDSM-Ax-7 scale removed from calculation of the overall score.

10.3.6 Analysis of the Secondary Efficacy Endpoints

A gated, fixed-sequence testing procedure will be used in this protocol to control the overall familywise false positive error rate for the primary and secondary endpoints analyses. As described above, the primary analysis will be regarded as positive and the trial will be successful for the co-primary efficacy endpoints if both null hypotheses in Section 10.3.1 and Section 10.3.2 of no difference are rejected in favor of sofpironium bromide gel, 15% at the 2-sided 0.05 level of significance.

If both co-primary analyses yield statistically significant results in favor of the sofpironium bromide gel, 15% group, the three secondary efficacy endpoints specified in Section 10.2.3 will be tested in a fixed sequence in the order presented in Section 10.2.3. Testing will continue only if all previously tested null hypotheses have been rejected at the 2-sided alpha=0.05 significance level in favor of sofpironium bromide gel, 15%.

The HDSM-Ax-7 1-point improvement responder secondary endpoint analysis will be conducted using the same logistic regression model as that used for the HDSM-Ax-7 co-primary efficacy analysis. For the composite endpoints, both baseline HDSM-Ax-7 score and baseline GSP value will be included as covariates.

10.3.7 Analysis of Exploratory Efficacy Endpoints

PGI-S and PGI-C endpoints will be analyzed using a Cochran-Mantel-Haenszel test. All other exploratory efficacy endpoints that involve a proportion of responders will be analyzed using methods similar to what was described for the HDSM-Ax-7 co-primary endpoint. All other exploratory endpoints that involve a change from baseline to a single timepoint will be analyzed using methods similar to what is described for the GSP co-primary endpoint. P-values for exploratory efficacy endpoints will be provided for descriptive purposes only and no formal hypothesis testing will occur. All exploratory efficacy analyses will be based on available data and missing GSP and HDSM-Ax EOT data imputed.

10.3.8 Psychometric Analysis of the HDSM-Ax-7

In parallel to the traditional statistical analysis, psychometric evaluation of the HDSM-Ax-7 will be carried out to confirm the most appropriate HDSM-Ax-7 scoring algorithm and to examine internal validity, construct validity (i.e., examination of the magnitude of correlation between the HDSM-Ax total score and key variables such as Questions 4 and 5 of the HDSM-Ax-7, PGI-S, PGI-C, and GSP), stability, reliability, ability to detect change, and interpretability of clinical trial results.

The details regarding psychometric analyses will be described in a separate statistical analysis plan.

10.4 Safety Analyses

Safety assessments of interest are local tolerability assessments, AEs, laboratory evaluations, and vital signs.

Safety analysis will be performed by treatment received for the Safety Population. Treatment-emergent adverse event descriptions will be mapped to standard terms, i.e., Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. At each post-baseline visit, the number and proportion of subjects reporting any given TEAE will be tabulated cumulatively by severity; each subject will be counted only once according to the worst severity reported up to the current visit. Separate tables will be constructed for (a) all reported TEAEs, (b) protocol treatment-related TEAEs, (c) serious TEAEs, (d) TEAEs leading to protocol treatment discontinuation, (e) protocol treatment-related serious TEAEs, (f) severe TEAEs, (g) TEAEs leading to dose interruption, (h) TEAEs of special interest, and (i) anticholinergic TEAEs.

At each visit, local tolerability assessments will be descriptively summarized by severity. For any symptoms, subject severity is the worst severity of the two axillae.

An overall summary table will also be presented with subject incidences tabulated according to the worst severity experienced while on study. In addition, at each post-baseline visit, local tolerability will be summarized as cumulative shift tables versus baseline. Subject counts for each symptom will be cross-tabulated with baseline severity according to the maximum post-baseline severity reported for either axilla up to the current visit.

Laboratory parameters will be descriptively summarized (mean, standard deviation, median, minimum, maximum) for values obtained at Visit 1 and Visit 12. Whereas, vital signs will be summarized in a similar manner at each visit.

10.5 Sample Size

Sample size estimation was performed for the co-primary efficacy endpoints based on the results of a Phase 2b study (BBI-4000-CL-203):

- HDSM-Ax-7 responder analysis: 2-point improvement response rates of 29.8% and 53.7% were assumed for the vehicle and sofpironium bromide gel, 15% arms, respectively. The power is 0.95 with 116 subjects per arm and a total of 232 subjects.
- GSP: using rank-transformed GSP data for change from baseline to EOT, a difference of 16.6 in mean ranks between the vehicle and sofpironium bromide gel, 15% arms, with a pooled standard deviation of approximately 39.5, was used for this purpose. Normal approximation yielded a sample size estimate of 296 subjects for the study, 148 each arm, in order to achieve 0.95 power for the GSP co-primary endpoint.

A chi-square test for the HDSM-Ax-7 endpoint and a two-sample t-test for the GSP endpoint were used to estimate the above sample size and power for each endpoint. With approximately 300 evaluable subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP).

Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment.

Additionally, sample size estimation was also performed using non-rank-transformed GSP data. An expected mean treatment difference of 73 mg with a pooled standard deviation of approximately 170 was used for this purpose. This yielded a reduced sample size estimate compared with the target of 300 subjects completing the co-primary efficacy assessments in order to achieve 0.95 power for GSP, further indicating that our sample size estimations are conservative.

11 STUDY ADMINISTRATION PROCEDURES

11.1 Subject Entry Procedures

11.1.1 Overview of Entry Procedures

Subjects with hyperhidrosis as defined by the criteria in Sections 4.2 and 4.3 (inclusion/exclusion criteria) will be considered for entry into this study.

11.1.2 Informed Consent and Subject Privacy

The study will be discussed with the subject, and a subject wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The subject must also give Authorization for Use and Release of Health and Research Study Information and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

11.1.3 Method for Assignment to Study Product Groups

All subjects who have signed an ICF will receive a 8-digit subject screening number composed of a 1-digit study number (1), a 3-digit site number, followed by a 4-digit sequentially assigned number starting at 0001, at each site. For instance, the first subject from site 001 will have 10010001 as their assigned subject screening number; the subsequent subject from this site will have 10010002 as their assigned subject screening number. The first subject from site 002 will have 10020001 as their assigned subject screening number; the subsequent subject from this site will have 10020002 as their assigned subject screening number. This number will be unique to each subject and will be used to identify the subject throughout the study.

The randomization for this study will be stratified by investigator site. Therefore, each site will be treated as a block and a randomization schedule will be prepared in order to balance the 1:1 treatment assignment within the site. Randomization details, including block size, will be prespecified in a randomization plan.

After subjects qualify for the study (as determined by the Investigator at the Screening/Rescreening Visits), they will be randomized to sofpironium bromide, 15% or vehicle gel, and notified that their screening number becomes their post-randomization subject number. Each kit carton will contain a treatment plastic pump, which will be labeled with a unique bottle number displayed on the label. A kit will be selected from inventory and dispensed to the subject after the proper prep/priming operation (see Section 5.2).

The next eligible subject will be assigned the next available randomization slot from the randomization list queue. In this manner, eligible subjects will be randomized to the investigational product in accordance with the site-specific randomization schedule. After obtaining the kit numbers assigned from the EDC system, the Investigator will document the kit numbers dispensed to the subject by tearing off the perforated portion of the carton label and placing it on the study subject source document.

Approximately 350 subjects will be randomized to receive either sofpironium bromide gel, 15%, or vehicle gel (placebo) in a ratio of 1:1.

11.2 Compliance with Protocol

At each post-baseline visit, the following activities will occur to ensure compliance with the protocol:

- Subjects will be asked whether they have used the investigational product as instructed.
- Subjects will be reminded to perform ONE FULL pump actuation and use the gel expressed per application to each axilla and asked whether they experienced any problems dispensing the investigational product.
- Subjects will be asked whether they used any other products on their axillae.
- Site staff will review concomitant medication use since the previous visit and determine whether any concomitant medication use qualifies as a protocol deviation
- At each post-baseline visit until EOT, site staff will collect the dispensing container from the subject, then weigh and record the weight of the used container.

11.3 Study Termination

The study may be stopped at a study site at any time by the site Investigator, after first notifying the Sponsor and discussing the reason(s) for stopping the study. Brickell Biotech, Inc. may stop the study with appropriate notification.

12 ADMINISTRATIVE ISSUES

12.1 Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrollment of subjects begins.

12.2 Protection of Human Subjects

12.2.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each subject prior to any study-related procedures. Potential subjects will be screened within 45 days prior to Visit 4 (Rescreening/Baseline) to assess their eligibility to enter the study. Only eligible subjects with axillary hyperhidrosis will be enrolled.

12.2.2 Compliance with IRB Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103). The Investigator must obtain approval from a properly constituted IRB prior to initiating the study and re-approval or review at least annually. Brickell Biotech, Inc. is to be notified immediately if the responsible IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB correspondence with the Investigator must be provided to Brickell Biotech, Inc.

12.2.3 Compliance with Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines, e.g., the ICH Guideline on GCP.

12.3 Changes to the Protocol

The Investigator should not implement any deviation from or changes to the protocol without approval by Brickell Biotech, Inc. and prior review and documented approval/favorable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

12.4 Subject Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the investigational product may ultimately be marketed, but a subject's name will not be disclosed in these documents. A subject's name may be disclosed to the Sponsor of the study, Brickell Biotech, Inc., the governing health authorities, or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

12.4.1 Subject Privacy

Written authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, in accordance with the applicable privacy requirements (e.g., HIPAA).

12.5 Documentation

12.5.1 Source Documents

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's subject study files, as well as the results of diagnostic tests. The Investigator's copy of the CRF serves as part of the Investigator's record of a subject's study-related data.

12.5.2 Electronic Case Report Form Completion

The Investigator is responsible for ensuring that data are properly recorded on each subject's eCRFs and related documents. The eCRFs are to be completed in a timely manner as defined in the clinical study agreement, or as otherwise specified by Brickell Biotech.

12.5.3 Retention of Documentation

All study-related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of CRFs should be maintained on file.

The Sponsor-specific essential documents should be retained until ≥2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or ≥2 years have elapsed since the formal discontinuation of clinical development of the investigational

product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

Brickell Biotech, Inc. requires that it be notified in writing if the Investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

12.6 Labelling, Packaging, Storage, and Return or Disposal of Investigational Product

12.6.1 Labeling/Packaging

The investigational product will be packaged, labeled, and supplied by Brickell Biotech, Inc. The product will be identified as an investigational compound for external use. The study number and a unique bottle number will be identified on the unit label of the product.

12.6.2 Storage of Investigational Product

The investigational product must be stored in a secure area with access limited to the Investigator and authorized site staff and administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in this protocol.

Investigational product should be stored at controlled room temperature, 68ºF to 77ºF (20ºC to 25ºC), with brief excursions permitted between 59°F to 86°F (15ºC to 30ºC). Maintenance of a temperature log (manual or automated) is required.

12.6.3 Clinical Supply Inventory

The investigational product must be prepared and dispensed only by an appropriately qualified person to subjects in the study. The investigational product is to be used in accordance with the protocol by subjects who are under the direct supervision of the Principal Investigator.

The Investigator or designated site staff are responsible for investigational product accountability, reconciliation, and record maintenance. The Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. Discrepancies are to be reconciled or resolved and documented.

12.6.4 Return or Disposal of Investigational Product

All investigational product (used and unused) will be returned to Brickell Biotech, Inc. or its designee for destruction.

12.7 Monitoring by the Sponsor

A representative of the Sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, size, and endpoints of the study. In the event of interruptions to site accessibility due to COVID-19 or other pandemics conditions, alternative means of monitoring the study documents may be implemented, as allowed by local and federal requirements, such as remote monitoring and/or data verification.

Authorized representatives of Brickell Biotech, Inc. and/or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the Investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

12.8 Publications

Brickell Biotech, Inc. as the Sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the Investigator and Brickell Biotech, Inc. personnel. Authorship will be established prior to the writing of the manuscript. No manuscripts regarding this study will be submitted without written authorization from Brickell Biotech, Inc.

13 REFERENCES

1. Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. *Arch Dermatol Res*. 2016;308(10):743-749.
2. Ayele BT, Lipkovich I, Molenberghs G, Mallinckrodt CH. A Multiple-Imputation-Based Approach to Sensitivity Analyses and Effectiveness Assessments in Longitudinal Clinical Trials. *J Biopharm Stat*. 2016;24(2):211-228.
3. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581–590.
4. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. US Department of Health and Human Services. Food and Drug Administration. July 2020. FDA website.

14 APPENDICES

APPENDIX 1: GRAVIMETRICALLY MEASURED SWEAT PRODUCTION

Method: ***Axilla Filter Paper Gravimetric Sweat Production Measurements***

Set Up

IMPORTANT: Make sure that you distinguish each gravimetric collection packet Right (R) from Left (L) throughout the gravimetric measurement (i.e., during set up, measurement).

- Clip or shave axilla hair if present. Use an electric razor or clippers so a short stubble (<1 mm) is present (blade shaving may irritate the skin or cause folliculitis; ok for men and women who use a manual razor routinely). Wash and clean the axilla to remove all loose hair or stubble. Towel dry the axilla(e).
- Place the subject in a room with controlled humidity and temperature between 20°C and 25°C (68°F to 77°F) for at least 30 minutes. During acclimation, the subject should remain in a semirecumbent position.
- Measurements will be done in the same room throughout the study.
- To the best of their ability, the same Study Site Staff member will perform the evaluation for each subject both within and across subjects. If this is not possible due to extenuating circumstances (e.g., vacation, illness, etc.), another qualified Study Site Staff Member cross-trained by the originally assigned staff member may perform these activities.
- Refer to the detailed study training manual and video for step-by-step directions.

Filter Paper Measurement

- Prepare the cotton towel, filter paper, and conical tube for the assessment.
- Place one filter paper and the conical tube with lid on the Sponsor-provided balance sensitive to 1 mg and record its weight. Tare the weight of the filter paper and conical tube.
- Have subject assume a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- Dry the axilla gently with the cotton towel.
- Using talc-free gloves, place the preweighed filter paper in the center of the axilla against the subject's skin, and have the patient carefully fold their axilla down to hold the filter paper in place. Immediately start the timer for 5 minutes. Immediately after 5 minutes, ask the patient to lift his/her arm and gently lift the filter paper out of the axillary vault and place it into the conical tube and replace lid to avoid evaporative loss of fluid.
- Record the time and weight.
- Refer to detailed study training manual and video for step-by-step directions.

APPENDIX 2: HYPERHIDROSIS DISEASE SEVERITY MEASURE-AXILLARY (HDSM-AX©), ≥ 12 YEARS OF AGE (VERSION 1.3)

Hyperhidrosis Disease Severity Measure--Axillary©

(HDSM-Ax)*

INSTRUCTIONS: We are interested in finding out about your current experience with excessive **underarm** sweating.

- Please consider excessive sweating in your **underarms only** when selecting the answer to each question.
- For each statement, please provide the response that best describes your **experience since you woke up yesterday**.
- Please answer **ALL** questions even if some seem similar to others or seem irrelevant to you.

---

1. Since you woke up yesterday, how often did you experience the following while you were awake?
(Please select the number that best describes your experience.)

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4
b) Underarm sweating for no apparent reason?	0	1	2	3	4

2. Since you woke up yesterday, how severe was your experience with the following? (Please select the number that best describes your experience.)

	I did not experience this	Mild	Moderate	Severe	Very severe
a) Underarm sweating when you felt nervous, stressed or anxious?	0	1	2	3	4
b) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4

c) Underarm sweating after little or no physical exercise?	0	1	2	3	4
d) Underarm wetness?	0	1	2	3	4
e) Underarm sweating for no apparent reason?	0	1	2	3	4
f) Underarm sweating that was unmanageable?	0	1	2	3	4
g) Underarm sweating when you were cool?	0	1	2	3	4

3. Since you woke up yesterday, what was your experience with each of the following? (Please select the number that best describes your experience.)

	Not at all	Slight	Moderate	Strong	Very strong
a) Feeling the need to change clothes because of underarm sweating?	0	1	2	3	4
b) Feeling the need to wipe sweat from your underarms?	0	1	2	3	4

SUMMARY QUESTIONS (ANCHORS):

4. Since you woke up yesterday, how much of the time did you experience excessive underarm sweating while you were awake? (Please select the number that best describes your experience.)

0 None of the time

1 A little of the time

2 Some of the time

3 Most of the time

4 All of the time

5. How severe was your underarm sweating AT ITS WORST since you woke up yesterday? (Please select the number that best describes your experience.)

0	I did not have underarm sweating (i.e., completely dry)
1	I had underarm sweating but it was mild (i.e., slightly damp)
2	I had underarm sweating and it was moderate (i.e., damp)
3	I had underarm sweating and it was severe (i.e., wet)
4	I had underarm sweating and it was very severe (i.e., soaking)

6. Patient Global Impression of Severity (PGI-S)

Please choose the response below that best describes the severity of your underarm sweating over the past week.**

0 None
1 Mild
2 Moderate
3 Severe
4 Very severe

7. Patient Global Impression of Change (PGI-C)

Please choose the response below that best describes the overall change in your underarm sweating since you started taking the study medication. †

- ☐ Very much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Very much worse

* These HDSM-Ax questions can appear slightly different when administered in an electronic format.

**Administered as Question #6 of HDSM-Ax at each assessment

† Administered as Question #7 of HDSM-Ax at the Day 43 (EOT) visit only.

APPENDIX 3: HYPERHIDROSIS DISEASE SEVERITY MEASURE-AXILLARY, CHILD (≥9 TO <12 YEARS OF AGE)

HDSM-Ax Child (version 28 FEB 2018)*

INSTRUCTIONS: We are interested in finding out about your **underarm** sweating.

- Circle the best answer to each question.
  - Think about sweating in your **underarms only**.
  - Think about your sweating **this morning and yesterday**.
- Please answer **ALL** questions.

---

1. Since you woke up yesterday, how often did you have these things?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a) Damp or wet clothes from underarm sweating?	0	1	2	3	4
b) Underarm sweating for no reason?	0	1	2	3	4

2. Since you woke up yesterday, how much did you have these things?

	I did not have this	A tiny amount	A little	A lot	A great amount
a) Underarm sweating when you felt nervous, scared, or worried?	0	1	2	3	4
b) Damp or wet clothing from underarm sweating?	0	1	2	3	4
c) Underarm sweating after sitting quietly?	0	1	2	3	4
d) Underarm wetness?	0	1	2	3	4
e) Underarm sweating for no reason?	0	1	2	3	4
f) Underarm sweating that you could not hide?	0	1	2	3	4
g) Underarm sweating when you were not hot?	0	1	2	3	4

3. Since you woke up yesterday, how much did you want to do these things?

	Not at all	A tiny amount	A little	A lot	A great amount
a) Change clothes because of underarm sweating?	0	1	2	3	4
b) Wipe sweat from your underarms?	0	1	2	3	4

4. Since you woke up yesterday, how much of the time did you have underarm sweating?

0 None of the time

1 A little of the time

2 Some of the time

3 Most of the time

4 All of the time

5. Describe your underarm sweating AT ITS WORST since you woke up yesterday?

0 I did not have underarm sweating

1 I had a tiny amount of underarm sweating

2 I had some underarm sweating

3 I had a lot of underarm sweating

4 I had a great amount of underarm sweating

6. Patient Global Impression of Severity (PGI-S)

Please choose the response below that best describes the severity of your underarm sweating over the past week.**

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

7. Patient Global Impression of Change (PGI-C)

Please choose the response below that best describes the overall change in your underarm sweating since you started taking the study medication. †

- ☐ Very much better
- ☐ Moderately better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Very much worse

* These HDSM-Ax questions can appear slightly different when administered in an electronic format.
**Administered as Question #6 of HDSM-Ax at each assessment

† Administered as Question #7 of HDSM-Ax at the Day 43 (EOT) visit only

APPENDIX 4: DERMATOLOGY LIFE QUALITY INDEX-AXILLA; FOR SUBJECTS ≥17 YEARS OF AGE

DERMATOLOGY LIFE QUALITY INDEX-Axilla

The aim of this questionnaire is to measure how much the SWEATING in your underarms has affected your life OVER THE LAST WEEK.

Please tick one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your **underarm skin** been?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your **underarm sweating**?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
3.	Over the last week, how much has your **underarm sweating** interfered with you going **shopping** or looking after your **home** or **garden**?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒
4.	Over the last week, how much has your underarm **sweating** influenced the **clothes** you wear?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒

5.	Over the last week, how much has your **underarm sweating** affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
6.	Over the last week, how much has your **underarm sweating** made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
7.	Over the last week, has your **underarm sweating** prevented you from **working** or **studying**?	Yes No Not relevant	❒ ❒ ❒
	If "No", over the last week how much has your **underarm sweating** been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒
8.	Over the last week, how much has your underarm **sweating** created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒

9	Over the last week, how much has your **underarm sweating** caused any **sexual difficulties**?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒
10.	Over the last week, how much of a problem has the **treatment** for your **underarm sweating** been, for example by making your home messy, or by taking up time?	Very much	❒
		A lot	❒
		A little	❒
		Not at all	❒
		Not relevant	❒

Please check that you have answered EVERY question. Thank you.

APPENDIX 5: TOLERABILITY ASSESSMENTS

These assessments are to be performed for each axilla individually. The designation of "Right Axilla" or "Left Axilla" in the source documents and eCRFs refers to the subject's right and left axilla respectively in all cases. Subject assessments are to be performed prior to Investigator assessments.

Local Tolerability (Subject): As reported by the Subject to the Investigator, the severity of any symptoms of burning, stinging, or itching at the application-site within the previous 24 hours, and further any such symptoms persisting longer than 1 hour following study drug application, will be described specifically by severity using the following standardized scales:

Score	Burning	Stinging	Itching
0 = Absent	Normal, no discomfort	Normal, no discomfort	Normal, no discomfort
1 = Minimal	An awareness, but no discomfort	An awareness, but no discomfort	An awareness, but no discomfort
2 = Mild	Noticeable discomfort causing intermittent awareness	Noticeable discomfort causing intermittent awareness	Noticeable discomfort causing intermittent awareness
3 = Moderate	Noticeable discomfort causing continuous awareness	Noticeable discomfort causing continuous awareness	Noticeable discomfort causing continuous awareness
4 = Severe	Definite discomfort causing continuous awareness, interfering occasionally with normal daily activities	Definite discomfort causing continuous awareness, interfering occasionally with normal daily activities	Definite discomfort causing continuous awareness, interfering occasionally with normal daily activities

Local tolerability (Investigator): The Investigator will assess the drug application site for the existence of significant local symptoms. Significant local symptoms are defined as those not ordinarily observed following application of a topical product. The following standardized scales will be used to describe specifically the severity of any erythema or scaling:

Score	Scaling	Erythema
0 = Absent	No scaling	No redness
1 = Minimal	Fine scaling, barely perceptible	Faint red or pink coloration, barely perceptible
2 = Mild	Slight scaling, noticeable only with light scratching	Light red or pink coloration
3 = Moderate	Definitely noticeable scaling	Medium red coloration
4 = Severe	Extensive scaling	Beet red coloration

APPENDIX 6: STUDY DRUG APPLICATION & SUBJECT INSTRUCTIONS

Apply the investigational product every day, at night prior to bedtime as follows:

1. Expose the underarm areas and ensure they are dry. Do not wash the underarm areas for at least 30 minutes prior to application.
2. Hold the plastic applicator between the index and middle fingers and the thumb of the left hand. Carefully, by applying consistent pressure to the actuator with an index finger, dispense the gel of ONE FULL actuation onto the dome of the white plastic applicator.
3. Immediately apply study product to the right underarm area.
4. Distribute all the gel expressed using the plastic applicator in a way that covers all the underarm area where the hair grows by gently applying a layer of the product.
5. Repeat the procedure to apply the study product to the left underarm using the right hand.
6. Thoroughly wash both hands and rinse the plastic applicator.
7. Allow the study product to dry for 5 minutes before putting any clothes on the upper body.

Important information:

- The subject should sleep in a T-shirt or similar pajama to avoid touching the underarm area while sleeping.
- Subjects should maintain their underarm areas grooming habits as follows:
    - Do not shower, shave, or wash the underarm area for at least 8 hours AFTER study product application.
    - Shaving of the underarm area should be done at least 8 hours BEFORE study product application.
    - If the subject takes a shower or washes the underarm area at night, then it should be at least 30 minutes before study product application.
    - Subjects should ensure the underarm areas are dry prior to application of the study product.
- Subjects should not apply any other product to the axillary area (including Sponsor-provided non-antiperspirant deodorant) for at least 8 hours after study product application.
- The subject should use the applicator provided to avoid contact with skin of the hands. Special care should be taken to avoid contact of the gel with the eyes or mouth. Of note, hands should be washed after applying the gel to avoid possible skin and eye contact with the gel.
- The study product contains alcohol and is flammable. The subject should avoid fire, flames, or smoking during the application and until the gel has dried. The subject should not expose the container to fire, flames, or extreme heat.

On the day of all clinic study visits you may shower but are NOT permitted to:

- Apply any product to your axilla (including Sponsor-provided non-antiperspirant deodorant).
- Exercise.
- Consume caffeine containing food or beverage until the gravimetric assessments are completed.

SUBJECT INSTRUCTIONS

Please follow these instructions carefully. If you do not understand anything in these instructions, ask the study doctor for help. To contact the study staff, call the telephone number noted below if you have any questions:

Contact:_____ At:_____

If you participate in this study, you will be expected to:

- Follow the instructions you are given and come to the study center for all visits with the study doctor or study staff.
- Tell the study doctor or study staff about any changes in your health or the way you feel.
- Tell the study doctor or study staff if you want to stop being in the study at any time.
- Apply the study product each evening before bedtime.
- Not shower, shave, or wash the underarm area for at least 8 hours after study product application.
- Not shave underarm area at least 8 hours prior to applying study product in the evening.
- Do not apply any other product to the axillary area (including Sponsor-provided non-antiperspirant deodorant) for at least 8 hours after study product application.
- Be careful not to touch your eyes or mouth with the gel or with your hands while applying the gel.
- Use an acceptable method of birth control throughout the entire study if you are able to become pregnant.
- Not breastfeed while you are in the study (for applicable females).
- Wear a T-shirt while sleeping or similar pajama and avoid touching the underarm area.
- Not start any new medications or change your medications without approval from the study doctor.
- Not allow access to the study medication assigned to you to anyone beside the study staff.
- Store the study medications according to the instructions on the label.

IMPORTANT:

- The investigational product contains alcohol and is flammable.
- Avoid fire, flames, or smoking during the application and until the gel has dried.
- **Do not** expose the container to fire, flame, or extreme heat.

Bring your previously dispensed Study Drug container to the following clinic visits AFTER Visit 4 (Baseline): Visit 7 (Day 22) and Visit 12 (End of Treatment; Day 43).

APPENDIX 7: PROTOCOL AMENDMENTS

AMENDMENT 01 SUMMARY OF CHANGES

Change Number	Section # / Name	Details of Change
1	All pages of protocol	Header: Added the version number to the protocol number /01 (Protocol BBI-4000-CL-301/01 on all pages) Footer: Added the amendment date to all pages

Change Number	Section # / Name	Details of Change
2	Title Page	Added the date of amendment
	Original Text	**VERSION**: Original September 20, 2019
	Revised Text	**ORIGINAL PROTOCOL:** September 20, 2019 **AMENDMENT 01:** November 08, 2019

Change Number	Section # / Name	Details of Change
3	SYNOPSIS, Inclusion Criteria	Revised text regarding acceptable contraceptive methods, duration of contraception, and definition of postmenopausal.
	Original Text	6. Sexually active females of childbearing potential (FOCBP)* who are engaging in sexual activity that can cause pregnancy must agree to periodic pregnancy testing and use a medically acceptable method of contraception while receiving protocol assigned product. This includes perimenopausal women who are less than 12 months from their last menses. Acceptable contraceptive methods include the following: a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy); b. Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR c. Two forms of non-hormonal contraception, including intrauterine devices (≥1-week status post placement), or properly used

		barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents). * FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months in women ≥55 years of age).
	Revised Text	6. Sexually active females of childbearing potential (FOCBP)* who are engaging in sexual activity that can cause pregnancy must agree to periodic pregnancy testing and use a medically acceptable method of contraception for the duration of the study. This includes perimenopausal women who are less than 12 months from their last menses. Acceptable contraceptive methods include the following: a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy); OR b. Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR c. Non-hormonal contraception, including intrauterine devices (≥1-week status post placement), or properly used barrier methods (e.g., male or female condoms with or without spermicide, cervical cap/diaphragm with spermicide). * FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Change Number	Section # / Name	Details of Change
4	SYNOPSIS, Study Design	Revised the number of clinical sites from 80 to 65
	Original Text	Approximately 450 subjects, at approximately 80 clinical sites in the United States will be randomized to receive either sofpironium bromide gel, 15% or vehicle gel (placebo) in a balanced 1:1 ratio in order to obtain approximately 406 evaluable subjects at the end of study.
	Revised Text	Approximately 450 subjects, at up to approximately 65 clinical sites in the United States, will be randomized to receive either sofpironium bromide gel, 15% or vehicle gel (placebo) in a balanced 1:1 ratio in order to obtain approximately 406 evaluable subjects at the end of study.

Change Number	Section # / Name	Details of Change
5	SYNOPSIS, Study Design	Removed Hyperhidrosis Quality of Life Index from the list of assessments.
	Original Text	Gravimetric measurements of sweat production and patient-reported outcomes HDSM-Ax-7, Hyperhidrosis Quality of Life Index, and Dermatology Life Quality Index (DLQI) (via electronic clinical outcomes assessment [eCOA] technology) will be recorded during the study at predefined time points.
	Revised Text	Gravimetric measurements of sweat production and patient-reported outcomes HDSM-Ax-7 and Dermatology Life Quality Index (DLQI) (via electronic clinical outcomes assessment [eCOA] technology) will be recorded during the study at predefined time points.

Change Number	Section # / Name	Details of Change
6	Section 2, Study Design	Revised text to reflect the change in number of clinical sites from 80 to 65

	Original Text	Approximately 450 subjects at 80 clinical sites in the US will be enrolled to obtain approximately 406 evaluable subjects at the end of study.
	Revised Text	Approximately 450 subjects, at up to approximately 65 clinical sites in the US, will be enrolled to obtain approximately 406 evaluable subjects at the end of study.

Change Number	Section # / Name	Details of Change
7	Section 4.1, Number of Subjects	Revised text to reflect the change in number of clinical sites from 80 to 65
	Original Text	Approximately 450 subjects, at approximately 80 clinical sites, will be randomized to receive either sofpironium bromide gel, 15% or vehicle gel in a 1:1 ratio to obtain approximately 406 evaluable subjects at the end of study.
	Revised Text	Approximately 450 subjects, at up to approximately 65 clinical sites, will be randomized to receive either sofpironium bromide gel, 15% or vehicle gel in a 1:1 ratio to obtain approximately 406 evaluable subjects at the end of study.

Change Number	Section # / Name	Details of Change
8	Section 4.2, Inclusion Criteria	Revised text regarding acceptable contraceptive methods, duration of contraception, and definition of postmenopausal.
	Original Text	6. Sexually active females of childbearing potential (FOCBP)* who are engaging in sexual activity that can cause pregnancy must agree to periodic pregnancy testing and use a medically acceptable method of contraception while receiving protocol assigned product. This includes perimenopausal women who are less than 12 months from their last menses. Acceptable contraceptive methods include the following: a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy);

		b. Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR c. Two forms of non-hormonal contraception, including intrauterine devices (IUD; ≥1 week status post placement), or properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents). * FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women ≥55 years of age).
	Revised Text	6. Sexually active females of childbearing potential (FOCBP)* who are engaging in sexual activity that can cause pregnancy must agree to periodic pregnancy testing and use a medically acceptable method of contraception for the duration of the study. This includes perimenopausal women who are less than 12 months from their last menses. Acceptable contraceptive methods include the following: a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy); OR b. Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR c. Non-hormonal contraception, including intrauterine devices (IUD; ≥1 week status post placement), or properly used barrier methods (e.g., male or female condoms with or without spermicide, cervical cap/diaphragm with spermicide). * FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy,

		bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Change Number	Section # / Name	Details of Change
9	Section 7.1, Time and Events Table	Table footnote 12 updated to reflect changes regarding acceptable contraceptive methods and definition of postmenopausal.
	Original Text	[12] FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months in women ≥55 years of age).
	Revised Text	[12] FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Change Number	Section # / Name	Details of Change
10	Section 8.1.3, Clinical Laboratory Assessments	Additional assessments added to the Routine Urinalysis Table, and specific gravity grouped with these additional assessments
	Original Text	pH, glucose, protein, blood and ketones by dipstick
	Revised Text	Bilirubin, color, appearance, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, and urobilinogen

Change Number	Section # / Name	Details of Change
11	Section 8.1.3, Clinical Laboratory Assessments	Text in other screening tests section revised to reflect changes to the definition of postmenopausal
	Original Text	* Females of childbearing potential for this study includes any female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral

		oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women ≥55 years of age).
	Revised Text	* Females of childbearing potential for this study includes any female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Change Number	Section # / Name	Details of Change
12	Section 9.5, Pregnancy Reporting	Changed occurrences of the word "effective" to "acceptable" when describing adequacy of contraception

Change Number	Section # / Name	Details of Change
13	Section 9.5, Pregnancy Reporting	Text revised to reflect changes in criteria for acceptable contraception and definition of postmenopausal.
	Original Text	FOCBP must agree to periodic pregnancy testing and use a medically acceptable method of contraception while receiving protocol-assigned product. This includes perimenopausal women who are <12 months from their last menses. Acceptable contraceptive methods include the following: • Abstinence for the duration of the study or where partner is sterile (e.g., vasectomy) is acceptable form of contraception; • Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR • Two forms of non-hormonal contraception, including IUD (≥1-week status post placement) or properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents). * FOCBP for this study includes any premenopausal female capable of becoming

		pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months in women ≥55 years of age).
	Revised Text	FOCBP must agree to periodic pregnancy testing and use a medically acceptable method of contraception for the duration of the study. This includes perimenopausal women who are <12 months from their last menses. Acceptable contraceptive methods include the following: • Abstinence for the duration of the study or where partner is sterile (e.g., vasectomy); OR • Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR • Non-hormonal contraception, including IUD (≥1-week status post placement) or properly used barrier methods (e.g., male or female condoms with or without spermicide, cervical cap/diaphragm with spermicide). * FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months).

Change Number	Section # / Name	Details of Change
14	Appendix 1	Revised text under set up section for gravimetrically measured sweat production methods
	Original Text	The same Study Site Staff member will perform the evaluation for each subject both within and across subjects. If this is not possible due to extenuating circumstances (e.g., vacation, illness, etc.), another

		qualified Study Site Staff Member cross-trained by the originally assigned staff member may perform these activities.
	Revised Text	To the best of their ability, the same Study Site Staff member will perform the evaluation for each subject both within and across subjects. If this is not possible due to extenuating circumstances (e.g., vacation, illness, etc.), another qualified Study Site Staff Member cross-trained by the originally assigned staff member may perform these activities.

Change Number	Section # / Name	Details of Change
15	Appendix 7	Added new Appendix 7 to detail changes made in AMENDMENT 01

AMENDMENT 02 SUMMARY OF CHANGES

Change Number	Section # / Name	Details of Change
1	Section 10.5, Sample Size	Text revised to reflect changes in the sample size calculation. Corresponding text in the synopsis and the following sections from the main body text revised accordingly: Section 2, Study Design; Section 4.1, Number of Subjects; and Section 11.1.3, Method for Assignment to Study Product Groups.
	Original Text	Based on analysis of results from a previous Phase 2b study (CL-203), the following treatment differences (and variation) are expected in this protocol for the co-primary efficacy endpoints: • HDSM-Ax-7 responder analysis: an expected treatment difference of 23.9% with a reference (vehicle group) response rate of approximately 29.8%. However, to be conservative, the lower limit of a 1-sided 75% confidence interval for the difference estimate, 18%, was used for sample size and power estimation. • GSP: an expected mean treatment difference of 73 mg for the continuous measurement data, with a pooled standard deviation of approximately 170. However, to be conservative, the lower limit of a 1-sided 62.5% confidence interval for the difference estimate, 61 mg, was used for sample size and power estimation. A chi-square test for the HDSM-Ax-7 endpoint and a two-sample t-test for the GSP endpoint were used to estimate power for each endpoint. It is estimated that 450 total subjects will need to be randomized (in a 1:1 allocation) with 406 subjects completing the co-primary efficacy assessments (approximately 10% drop-out rate). With 406 evaluable subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary endpoints

		simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP). Additionally, sample size estimation was also performed using rank-transformed GSP data. A difference of 16.6 in mean ranks with a pooled standard deviation of approximately 42 was used for this purpose. This yielded a reduced sample size estimate compared with the target of 406 subjects completing the co-primary efficacy assessments in order to achieve 0.95 power for GSP, further indicating that our sample size estimations are conservative.
	Revised Text	Sample size estimation was performed for the co-primary efficacy endpoints based on the results of a Phase 2b study (BBI-4000-CL-203): • HDSM-Ax-7 responder analysis: 2-point improvement response rates of 29.8% and 53.7% were assumed for the vehicle and sofpironium bromide gel, 15% arms, respectively. The power is 0.95 with 116 subjects per arm and a total of 232 subjects. • GSP: using rank-transformed GSP data for change from baseline to EOT, a difference of 16.6 in mean ranks between the vehicle and sofpironium bromide gel, 15% arms, with a pooled standard deviation of approximately 39.5, was used for this purpose. Normal approximation yielded a sample size estimate of 296 subjects for the study, 148 each arm, in order to achieve 0.95 power for the GSP co-primary endpoint. With approximately 300 evaluable subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP).

		Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment.

Change Number	Section # / Name	Details of Change
2	Section 2, Study Design	The number of potential sites was changed from up to 65 to up to 45, and the number of subjects in each treatment arm was adjusted to 175. Corresponding text in the synopsis and Section 4.1, Number of Subjects also revised.
	Original Text	Approximately 450 subjects, at up to approximately 65 clinical sites in the US, will be enrolled to obtain approximately 406 evaluable subjects at the end of study. Subjects will be randomized 1:1 to receive sofpironium bromide gel, 15% or vehicle gel (225 subjects dosed with 15% gel and 225 subjects dosed with vehicle gel).
	Revised Text	Approximately 350 subjects, at up to approximately 45 clinical sites in the US, will be enrolled to obtain approximately 300 evaluable subjects at the end of study. Subjects will be randomized 1:1 to receive sofpironium bromide gel, 15% or vehicle gel (175 subjects dosed with 15% gel and 175 subjects dosed with vehicle gel).

AMENDMENT 03 SUMMARY OF CHANGES

Change Number	Section # / Name	Details of Change
1	SYNOPSIS, Study Objectives; Section 2, Study Design; Section 3, Study Objectives and Assessments	Text was revised in multiple sections to specify *primary* axillary hyperhidrosis as the indication throughout the protocol.
	Original Text	… subjects with axillary hyperhidrosis.
	Revised Text	…subjects with primary axillary hyperhidrosis.

Change Number	Section # / Name	Details of Change
2	SYNOPSIS, Inclusion Criteria, Footnote 1	Text was revised to indicate imputation details regarding HDSM-Ax-7 values.
	Original Text	Subjects must answer all of the 7 sub items to be evaluable for the HDSM-Ax-7 scale assessment.
	Revised Text	For each of the HDSM-Ax sub-items, missing values at EOT will be imputed. HDSM-Ax-7 at EOT will be derived from the imputed values.

Change Number	Section # / Name	Details of Change
3	SYNOPSIS, Statistical Methods, Efficacy	Details were added regarding normality testing and the use of rank-transformed versus continuous GSP data.
	Original Text	The GSP co-primary endpoint will be analyzed using a rank based analysis of covariance (ANCOVA) model with fixed effects for treatment, baseline ranked GSP, and analysis center.
	Revised Text	The GSP co-primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects for treatment, baseline ranked GSP, and analysis center. The ANCOVA may use rank-transformed or continuous data, pending the outcome of the Shapiro Wilk Normality test. The normality test will be performed prior to multiple imputation and separately for each arm. Should the normality assumption be violated for either arm, the

		primary analysis will use rank-transformed GSP data. If the normality assumption holds for both arms, the primary analysis will use continuous GSP data.

Change Number	Section # / Name	Details of Change
4	SYNOPSIS, Statistical Methods, Safety	Additional TEAE tables were included in the safety analyses.
	Original Text	Separate tables will be constructed for (a) all reported TEAEs, (b) protocol treatment-related TEAEs, (c) serious TEAEs, and (d) TEAEs leading to protocol treatment discontinuation,
	Revised Text	Separate tables will be constructed for (a) all reported TEAEs, (b) protocol treatment-related TEAEs, (c) serious TEAEs, (d) TEAEs leading to protocol treatment discontinuation, (e) protocol treatment-related serious TEAEs, (f) severe TEAEs, (g) TEAEs leading to dose interruption, (h) TEAEs of special interest, and (i) anticholinergic TEAEs.

Change Number	Section # / Name	Details of Change
5	SYNOPSIS, Statistical Methods, Sample Size and Power Estimation	Additional details were added regarding sample size estimation.
	Original Text	With approximately 300 evaluable subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP). Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment.
	Revised Text	A chi-square test for the HDSM-Ax-7 endpoint and a two-sample t-test for the GSP endpoint were used to estimate the above sample size and power for each endpoint. With approximately 300 evaluable

		subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP). Additionally, sample size estimation was also performed using non-rank-transformed GSP data. An expected mean treatment difference of 73 mg with a pooled standard deviation of approximately 170 was used for this purpose. This yielded a reduced sample size estimate compared with the target of 300 subjects completing the co-primary efficacy assessments in order to achieve 0.95 power for GSP, further indicating that our sample size estimations are conservative. Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment.

Change Number	Section # / Name	Details of Change
6	Section 1, Background and Clinical Rationale, Prior Human Experience	Text was updated to reflect the most current number of subject exposures; additionally, text was deleted pertaining to previously ongoing studies, which have now been completed.

Change Number	Section # / Name	Details of Change
7	Section 7, Procedures	Text was added following the introductory paragraphs in Section 7 to specify that some assessments may be conducted remotely due to COVID-19-related restrictions.
	Revised Text	In the event of restrictions due to COVID-19, or any other pandemic, the Sponsor may, with IRB approval where required, during the study implement some or all study assessments and procedures associated with patient visits to be conducted remotely or by home visits (per FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health

		Emergency, March 2020) when the patients' ability to visit investigator sites is impacted.

Change Number	Section # / Name	Details of Change
8	Section 10.2.2, Co-Primary Efficacy Endpoints	Imputation methods for the HDSM-Ax-7 endpoint were revised.
	Original Text	The mean will be derived by taking the sum of 7 item scores and dividing it by 7. Subjects must answer all of the 7 sub-items to be evaluable for the HDSM-Ax-7 endpoint. Data will be considered missing for non-evaluable subjects.
	Revised Text	The mean will be derived by taking the sum of 7 item scores and dividing it by 7. For each of the HDSM-Ax sub-items, missing values at EOT will be imputed as described briefly in Section 10.3.1. HDSM-Ax-7 at EOT will be derived from the imputed values. Further details on imputation methods will be provided in the SAP.

Change Number	Section # / Name	Details of Change
9	Section 10.2.4, Exploratory Efficacy Endpoints	Additional exploratory endpoints were included.
	Revised Text	• The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax Question 4 score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57. • The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax Question 5 score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.

Change Number	Section # / Name	Details of Change
10	Section 10.3, Analysis Methods	Text was added specifying that missing values will be imputed.
	Original Text	The primary efficacy analysis will be performed on the ITT population.

	Revised Text	The primary efficacy analysis will be performed on the ITT population with missing values imputed.

Change Number	Section # / Name	Details of Change
11	Section 10.3.1, Primary and Secondary Analysis of the HDSM-Ax-7 Co-Primary Endpoint	Revisions were made to the text pertaining to the imputation model.
	Original Text	If a subject is missing Visit 4 (Day 1) value, Visit 1 (Screening) value will be used as Baseline. If a subject is missing Day 43 value, the closest (in time) available non-missing HDSM-Ax-7 value from Day 41 (±2 days) or Day 42 (±2 days) will be used as the first level of imputation. Should none of the Days 41, 42, and 43 values be available, multiple imputations of missing EOT HDSM-Ax-7 score will be performed on the sofpironium bromide, 15% arm values using a control-based imputations (CBI) methodology (see Section 10.3.4). Multiple imputations assuming missing at random will be performed for missing data for vehicle subjects.
	Revised Text	Imputation will be item-level. If a subject is missing values for any of items 1a, 1b, 2a, 2b, 2c, 2d, or 2e at Visit 4 (Day 1), the Visit 1 (Screening) value will be used as Baseline. If the Visit 1 (Screening) value is also missing, the subject will be excluded from all HDSM-Ax-7 change from baseline analyses. If a subject is missing Day 43 value, the closest (in time) available non-missing value from Day 41 (±2 days) or Day 42 (±2 days) will be used as the first level of imputation. Should none of the Days 41, 42, and 43 values be available, multiple imputations of missing EOT item-level scores will be performed on the sofpironium bromide gel, 15% arm values using a control-based imputations (CBI) methodology (see

		Section 10.3.4). Multiple imputations assuming missing at random will be performed for missing data for vehicle subjects. The HDSM-Ax-7 score will be calculated using the imputed item-level values. Further details on imputation methods will be provided in the SAP.

Change Number	Section # / Name	Details of Change
12	Section 10.3.1, Primary and Secondary Analysis of the HDSM-Ax-7 Co-Primary Endpoint	Details regarding site poolability were added in the estimand sub-section.
	Revised Text	In addition, a separate site poolability analysis will be performed with analysis center-by-treatment interaction terms added to the primary analysis model. An overall $p < 0.10$ for the combined interaction terms will be regarded as an indication of potential heterogeneity among the analysis centers. A mixed model analysis will then be performed with analysis center as a random effect to account for the potential heterogeneity.

Change Number	Section # / Name	Details of Change
13	Section 10.3.2, Primary and Secondary Analyses of the GSP Co-Primary Endpoint	Text was added describing the methods for using either rank-based or continuous data for the co-primary endpoint analysis.
	Revised Text	Either rank-based GSP change from baseline to EOT or continuous GSP change from baseline to EOT will be analyzed. The GSP assessment is known to be a highly variable measure, and as such, the Shapiro Wilk test of normality will be performed to determine if the co-primary endpoint will be continuous or rank transformed. The normality test will be performed prior to multiple imputation for missing data and separately for each

		arm. Should the normality assumption be violated for either arm, the co-primary endpoint will be analyzed using rank-transformed GSP data. If the normality assumption holds for both arms, then the co-primary endpoint will be analyzed using continuous GSP data.

Change Number	Section # / Name	Details of Change
14	Section 10.3.2, Primary and Secondary Analyses of the GSP Co-Primary Endpoint	Text was revised to indicate changes to the imputation method regarding the use of continuous or ranked data.
	Original Text	**Imputation Model:** Data from subjects (see Section 10.3.3) meeting the criterion for "outlier" will be removed from imputation sampling database (i.e., data for vehicle patients) prior to missing data imputation. From the remaining imputation sampling database of continuous GSP measurements, multiple imputations of missing EOT sofpironium bromide, 15% arm GSP values will be performed using a CBI methodology (see Section 10.3.4). Multiple imputations assuming MAR will be performed for missing EOT data vehicle subjects. **Analysis Model:** ANCOVA model (either non-ranked or ranked, pending outcome of normality test) **Fixed effects:** The following fixed effects are planned: • Treatment (class effect: sofpironium bromide gel, 15% group, vehicle group) • Baseline ranked GSP • Analysis center (see Section 10.3.3)
	Revised Text	**Imputation Model:** Imputation will be done using continuous data prior to rank-transformation, should the normality assumption be violated. For continuous data, subjects with results (see Section 10.3.3) meeting the criterion for "outlier" will be removed from imputation sampling database (i.e.,

		data for vehicle patients) prior to missing data imputation. From the remaining imputation sampling database of continuous GSP measurements, multiple imputations of missing EOT sofpironium bromide, 15% arm GSP values will be performed using a CBI methodology (see Section 10.3.4). Multiple imputations assuming MAR will be performed for missing EOT data vehicle subjects. Further details on multiple imputations will be provided in the SAP. **Analysis Model:** ANCOVA model (either non-ranked or ranked, pending outcome of normality test) **Fixed effects:** The following fixed effects are planned: • Treatment (class effect: sofpironium bromide gel, 15% group, vehicle group) • •Baseline GSP (either non-ranked or ranked, pending outcome of normality test) • •Analysis center (see Section 10.3.3)

Change Number	Section # / Name	Details of Change
15	Section 10.3.2, Primary and Secondary Analyses of the GSP Co-Primary Endpoint	Text in (a) was revised to indicate changes to the imputation method regarding the use of continuous or ranked data, and text was added to (c) regarding site poolability analysis.
	Original Text	(a) Using the same methodology as described above, an ANCOVA analysis will be performed for either the non-rank transformed, continuous GSP data.
	Revised Text	(a) Using the same methodology as described above, an ANCOVA analysis will be performed for either the non-rank transformed, continuous GSP data or the rank transformed GSP data, pending the results of the normality test. If the normality assumption is violated and the rank-transformed data are used as the co-primary endpoint, analysis of the continuous data will be supportive. If the normality assumption holds and the continuous

		data are used as the co-primary endpoint, then analysis of the rank-transformed data will be supportive. (b)…. (c) For the primary endpoint of either ranked or continuous GSP (pending normality test results), a separate, site poolability analysis will be performed with analysis center-by-treatment interaction terms added to the primary analysis model. An overall p < 0.10 for the combined interaction terms will be regarded as an indication of potential heterogeneity among the analysis centers. A mixed model analysis will then be performed with analysis center as a random effect to account for the potential heterogeneity.

Change Number	Section # / Name	Details of Change
16	Section 10.3.3, Method of Pooling Sites to Generate Analysis Centers	Text was revised to indicate details regarding pooling of sites.
	Original Text	The lowest enrolling site will be combined with the largest enrolling site that does not meet the minimum requirement, and then the second lowest enrolling site and the second largest enrolling site will be combined, and so on. Further combining will be done until all analysis centers have at least 10 subjects. All analyses that are controlled for site will use this analysis center designation.
	Revised Text	For sites with <10 enrollments, the lowest enrolling site will be combined with the largest enrolling site, and then the second lowest enrolling site and the second largest enrolling site will be combined, and so on. Further combining will be done as necessary until all analysis centers have at least 10 subjects. All analyses that are controlled for site will use this analysis center designation. Site poolability will also be assessed as described in Sections 10.3.1 and 10.3.2.
Change Number	**Section # / Name**	**Details of Change**

17	Section 10.3.5, Sensitivity Analyses of the Co-Primary Efficacy Endpoints	Text was added that specified increments used for the GSP co-primary endpoint for Sensitivity Analysis 4.
	Original Text	Missing values will be multiply imputed via this method with increasing Δ values. The GSP co-primary efficacy outcome analysis methodology will be applied to the imputed datasets and repeated until statistical significance no longer holds. The tipping point will be identified and the results will be summarized graphically. For the HDSM-Ax-7 co-primary endpoint, identical imputation methodology to that described above for the GSP will be applied to the HDSM-Ax-7 total scores, and the resulting values will be dichotomized into responders versus non-responders using the 2-point improvement criterion.
	Revised Text	Missing values will be multiply imputed via this method with increasing Δ values. A Δ increment of 5 mg will be used for this study. The GSP co-primary efficacy outcome analysis methodology will be applied to the imputed datasets and repeated until statistical significance no longer holds. The tipping point will be identified and the results will be summarized graphically. For the HDSM-Ax-7 co-primary endpoint, identical imputation methodology to that described above for the GSP will be applied to the HDSM-Ax-7 total scores, and the resulting values will be dichotomized into responders versus non-responders using the 2-point improvement criterion. A Δ increment of 0.5 (on a 0-4 scale) will be used for this study.

Change Number	Section # / Name	Details of Change
18	Section 10.3.5, Sensitivity Analyses of the Co-Primary Efficacy Endpoints	Details were added regarding the sensitivity analysis.
	Original Text	**Sensitivity Analysis 5:** A sensitivity analysis will be conducted to investigate whether any of the individual items in the HDSM-Ax-7 scale are

		overly influencing changes observed in the total score. The primary analysis for HDSM-Ax-7 will be repeated for each of the 7 individual items.
	Revised Text	**Sensitivity Analysis 5:** A sensitivity analysis will be conducted to investigate whether any of the individual items in the HDSM-Ax-7 scale are overly influencing changes observed in the total score. First, a subject will be counted as a responder if they achieve at least a 2-point improvement in the individual question from baseline to EOT. The logistic regression model for the primary analysis for HDSM-Ax-7 will be repeated for each of the 7 individual items, and each individual question will be analyzed separately. Secondly, one of the 7 items will be omitted, and the HDSM-Ax-7 total score will be calculated as the average of the remaining 6 items. The primary logistic regression analysis for 2-point improvement response rate will be performed on this 6-item scale. This process will be repeated 7 times, each time with a different item of the HDSM-Ax-7 scale removed from calculation of the overall score

Change Number	Section # / Name	Details of Change
19	Section 10.3.7, Analysis of Exploratory Efficacy Endpoints	Text was added to specify the method for PGI-S and PGI-C endpoints, and to clarify when imputation for missing data will be performed.
	Original Text	All exploratory efficacy endpoints that involve a proportion of responders will be analyzed using methods similar to what was described for the HDSM-Ax-7 co-primary endpoint. All other exploratory endpoints that involve a change from baseline to a single timepoint will be analyzed using methods similar to what is described for the GSP co-primary endpoint. P-values for exploratory efficacy endpoints will be provided for descriptive purposes only and no formal hypothesis testing will occur.
	Revised Text	PGI-S and PGI-C endpoints will be analyzed using a Cochran-Mantel-Haenszel test. All other exploratory efficacy endpoints that involve a

		proportion of responders will be analyzed using methods similar to what was described for the HDSM-Ax-7 co-primary endpoint. All other exploratory endpoints that involve a change from baseline to a single timepoint will be analyzed using methods similar to what is described for the GSP co-primary endpoint. P-values for exploratory efficacy endpoints will be provided for descriptive purposes only and no formal hypothesis testing will occur. All exploratory efficacy analyses will be based on available data and missing GSP and HDSM-Ax EOT data imputed.

Change Number	Section # / Name	Details of Change
20	Section 10.4, Safety Analyses	Additional items were included [(e) through (i)], which specify tabulated summaries to be produced for TEAEs. Additional text was added specifying the definition of subject severity.
	Revised Text	(e) protocol treatment-related serious TEAEs, (f) severe TEAEs, (g) TEAEs leading to dose interruption, (h) TEAEs of special interest, and (i) anticholinergic TEAEs…For any symptoms, subject severity is the worst severity of the two axillae.

Change Number	Section # / Name	Details of Change
21	Section 10.5, Sample Size	Additional details were included regarding estimation of sample size.
	Original Text	With approximately 300 evaluable subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP). Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment.
	Revised Text	A chi-square test for the HDSM-Ax-7 endpoint and a two-sample t-test for the GSP endpoint were used to estimate the above sample size and power for each endpoint. With approximately 300 evaluable

		subjects, the overall study power to demonstrate a statistically significant treatment effect (two-sided $p < 0.05$) for both co-primary efficacy endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP). Assuming missing data from approximately 15% of subjects, a total of 350 subjects will be targeted for enrollment. Additionally, sample size estimation was also performed using non-rank-transformed GSP data. An expected mean treatment difference of 73 mg with a pooled standard deviation of approximately 170 was used for this purpose. This yielded a reduced sample size estimate compared with the target of 300 subjects completing the co-primary efficacy assessments in order to achieve 0.95 power for GSP, further indicating that our sample size estimations are conservative.

Change Number	Section # / Name	Details of Change
22	Section 12.7, Monitoring by the Sponsor	Text was added to specify that alternative means of monitoring may be implemented due to COVID-19 conditions.
	Original Text	A representative of the Sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, size, and endpoints of the study. Authorized representatives of Brickell Biotech, Inc. and/or regulatory authority representatives will conduct on site visits to review, audit, and copy study-related documents. These representatives will meet with the Investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.
	Revised Text	A representative of the Sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose,

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