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A Multicenter, Randomized, Open-label, Phase 3 Long-term Safety Study of Topically Applied Sofpironium Bromide (BBI-4000) Gel, 5% and 15% in Subjects with Axillary Hyperhidrosis

PROTOCOL NUMBER:	BBI-4000-CL-303
NAME OF INVESTIGATIONAL PRODUCT:	Sofpironium Bromide (BBI-4000)
ORIGINAL PROTOCOL:	March 7, 2018
AMENDMENT 01:	May 15, 2018
SPONSOR:	Brickell Biotech, Inc. 5777 Central Ave., Suite 102 Boulder, CO 80301
PHASE:	3 (Long-term Safety Study; the Argyle Study)
IND NUMBER:	121,256
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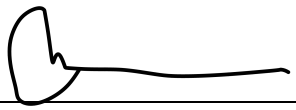
NCT03627468

SPONSOR SIGNATORY:



May 16 2018

Patricia Walker, MD, PhD
President and Chief Scientific Officer

Date

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices (GCPs), 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

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SYNOPSIS

Protocol Title

A Multicenter, Randomized, Open-label, Phase 3 Long-term Safety Study of Topically Applied Sofpironium Bromide (BBI-4000) Gel, 5% and 15% in Subjects with Axillary Hyperhidrosis

Study Objectives

Primary:

To evaluate the long-term safety and local tolerability of sofpironium bromide gel, 5% and 15% when applied topically in subjects with axillary hyperhidrosis.

Secondary:

- To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax©) in subjects with axillary hyperhidrosis.
- To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on patient reported Dermatology Life Quality Index (DLQI) in subjects with axillary hyperhidrosis.

Other:

- To evaluate the effect of topically applied sofpironium bromide gel, 5% and 15% on the Hyperhidrosis Quality of Life Index (HidroQoL©) in subjects with axillary hyperhidrosis. Only the first 100 subjects enrolled will complete this assessment.

Study Population

Subjects aged ≥12 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 ≥12 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 of 3 – 4 inclusive at both the Screening Visit (Visit 1) and Baseline Visit (Visit 2).

b. Symptoms of axillary hyperhidrosis for ≥6 months' duration prior to Baseline Visit (Visit 2).

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 (if the subject reaches 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)* must agree to periodic pregnancy testing and use a medically acceptable method of contraception while receiving protocol-assigned product. Acceptable contraceptive methods include the following:

a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy), is an acceptable form of contraception;

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).

Exclusion Criteria

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

1. In the Investigator's opinion, 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) within the specified timeframe for the treatment of axillary hyperhidrosis:

a. Botulinum toxin to the axillary area within 6 months of the Baseline Visit (Visit 2).

b. Axillary thermolysis, sympathectomy or surgical procedures of the axillary area at any time in the past.

c. Serotonergic agonist (or drugs that increase serotonin activity including SSRIs), beta-blocker, alpha-adrenergic agonist (clonidine), dopamine partial agonist or tricyclic antidepressant treatment within 28 days of the Baseline Visit (Visit 2). However, if a subject has been on a stable dose (in the opinion of the PI) 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; they may be included. Doses of these agents should not be altered during the course of the study.

d. Any topical treatment for hyperhidrosis, requiring a prescription, within 15 days of Baseline Visit (Visit 2).

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., IV, oral, inhaled, topical) within 28 days of the Baseline Visit (Visit 2).

4. Use of potent oral inhibitors of cytochrome P450 CYP3A & CYP2D6 and transporter inhibitors (OCT2/MATE1/MATE2) 14 days prior to the Baseline Visit (Visit 2). The use of topical antifungal medications is permitted if not applied in the treatment area. See Appendices 6 and 7.

5. Any oral or topical homeopathic or herbal treatment (i.e., alternative therapies such as sage tablets, chamomile, valerian root and St. John's Wort) within 7 days of the Baseline Visit (Visit 2).

6. Use of any cholinergic drug (e.g., bethanechol) within 15 days of the Baseline Visit (Visit 2).

7. Use of any anti-anxiety and/or anti-depressant, amphetamine product or drugs with known anticholinergic side effects is prohibited with the following exceptions:

a. If a subject 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; they may be included.

b. An amphetamine product may be allowed if the dose has been stable for ≥6 months without change in hyperhidrosis frequency or severity.

c. Drugs with known anticholinergic side effects (taken within the last 28 days), including dry mouth, 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 eCRF. The doses of these agents should not be altered during the course of the study.

8. Known causes of hyperhidrosis or known history of a condition that may cause hyperhidrosis (i.e., hyperhidrosis secondary to any known cause such hyperthyroidism, diabetes mellitus, medications, etc.).

9. Subjects with hyperhidrosis symptoms initiated or exacerbated with menopause.

10. Subjects with unstable type 1 or type 2 diabetes mellitus or thyroid disease, history of 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.

11. Known hypersensitivity to glycopyrrolate, anticholinergics, or any of the components of the topical formulation.

12. Subject is pregnant, lactating or is planning to become pregnant during the study.

13. Participating in a study of or used an investigational drug or device within 28 days prior to the Baseline Visit (Visit 2).

14. Any major illness within 28 days before the screening examination.

15. 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.

16. History or presence of supraventricular tachycardia, ventricular arrhythmias, atrial fibrillation or atrial flutter.

17. 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

A maximum of 300 subjects, at approximately 30 clinical sites, will be randomized to receive either sofpironium bromide gel, 5% or 15% in a 1:2 ratio to obtain approximately 150 subjects (50 subjects dosed with 5% gel and 100 subjects dosed with 15% gel) who have completed 48 weeks of dosing and 52 weeks of clinical assessments.

Subjects will apply the Investigational Product (sofpironium bromide gel, 5% or 15%); once daily at bedtime, to both axillae for 48 weeks.

Vital signs, local tolerability assessments (including burning, itching, dryness, scaling and erythema assessed using standardized scales), and adverse events will be collected at each visit. Urine pregnancy tests (UPT) for FOCBP will be taken throughout the course of the study and blood and urine samples will be

collected and analyzed at the Screening Visit and at Visit 5 (Week 6), Visit 10 (Week 24), and Visit 16 (Week 48) for routine hematology, chemistry, and urinalysis parameters. Patient-reported outcomes: HDSM-Ax and DLQI 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 24 Week and 48 Week (EOT) visits. HidroQoL will be recording during the study at baseline, Visit 3 (Week 2), and Visit 5 (Week 6); only the first 100 subjects enrolled will complete this asessment.

A total of 17 scheduled visits will take place over approximately 52 weeks.

Test Product, Dose, and Mode of Administration

5% or 15% sofpironium bromide (BBI-4000) gel topically applied to the axillae

Duration of Treatment

48 weeks (11 months) followed by a 4-week post-treatment visit (52 weeks)

Safety Assessments

- Adverse events
- Local tolerability assessments including burning, itching, dryness, scaling and erythema
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Laboratory tests (hematology, chemistry, and urinalysis) and pregnancy testing in FOCBP

Efficacy Assessments

The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%:

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

Additionally, HidroQoL assessment will be conducted as an exploratory analysis, as measured by the subject (for subjects ≥17 years of age). This assessment will be performed at baseline, Visit 3 (Week 2), and Visit 5 (Week 6) for only the first 100 subjects enrolled in the study.

Statistical Methods

Safety Analyses

Treatment emergent adverse event (TEAE) descriptions will be mapped to standard terms, i.e., 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 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, and (d) TEAEs leading to protocol treatment discontinuation.

At each visit, local tolerability (burning, itching, scaling, dryness and erythema at either axilla) will be described by severity. At each post-baseline visit, local tolerability will be summarized as cumulative shift

tables *vs*. 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 [SD], median, minimum, maximum) for values at each specified visit and for changes from screening at each subsequent measurement. In addition, for each post-baseline measurement, parameter status (low, normal, high) will also be summarized as shift tables *vs*. screening status.

Vital signs will be summarized similarly as for laboratory parameters but without shift tables.

Efficacy Analyses

For HDSM-Ax the mean of the items in sections No. 1, 2, and 3 (11 sub-items in total) will be used for analysis. The HDSM-Ax total score will be descriptively summarized (mean, SD, median, minimum, maximum) for values at each visit and for changes from baseline (average of screening and Day 0) at each subsequent visit. In addition, at each post-baseline visit, the proportions of subjects with a ≥1.0 point, ≥1.5-point, and ≥2-point decrease from baseline will be reported.

Change in the DLQI from baseline to Week 2, Week 6, Week 24, and Week 48 (EOT).

Exploratory Analysis

Change in the HidroQoL from baseline to Week 2 and Week 6 will be assessed. Only the first 100 subjects enrolled in the study will complete this assessment, and an interim analysis will be performed.

ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BBI-4000	Sofpironium bromide
BP	Blood pressure
BPH	Benign prostatic hyperplasia
Bpm	Beats per minute
BUN	Blood urea nitrogen
C	Celsius
Chem.	Chemistry
CFR	Code of Federal Regulations
Conmeds	Concomitant medications
CRF	Case Report Form
CRO	Contract Research Organization
DB20	Dimethiconol Blend 20
DLQI	Dermatology Life Quality Index
DLQI-Palm	Dermatology Life Quality Index-Palm
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
F	Fahrenheit
FDA	Food and Drug Administration
FOCBP	Female of Childbearing Potential
G	Grams
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GSP	Gravimetric Sweat Production
HDSM-Ax	Hyperhidrosis Disease Severity Measure-Axillary
HDSM-Palm	Hyperhidrosis Disease Severity Measure-Palm Scale
HDSS	Hyperhidrosis Disease Severity Scale

Heme.	Hematology
HidroQoL	Hyperhidrosis Quality of Life Index
HIPAA	Health Insurance Portability and Accountability Act
Hr	Hour
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
I/E	Inclusion and Exclusion Criteria
IEC	Institutional Ethics Committee
IND	Investigational New Drug
IP	Investigational product
IPM	Isopropyl myristate
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IV	Intravenous
Kg	Kilogram
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
mo.	Months
MUPK	Maximum use pharmacokinetics
NF	National Formulary
Ng	Nanogram
nM	Nanomolar
PGI-C	Patient Global Impression of Change

PGI-S	Patient Global Impression of Severity
PHIS	Palmar Hyperhidrosis Impact Scale
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SSRI	Selective serotonin re-uptake inhibitors
Temp	Temperature
US	United States of America
UPT	Urine Pregnancy Test
USP	United States Pharmacopeia
WBC	White blood cell

1 BACKGROUND AND CLINICAL RATIONALE

Sofpironium bromide (BBI-4000) is a novel soft-anticholinergic ester analog of glycopyrrolate in development for the topical treatment of 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. Please refer to the sofpironium bromide (BBI-4000) Investigator's Brochure for more information.

Hyperhidrosis is a disorder of excessive sweating beyond what is expected for thermoregulatory needs and environmental conditions. Primary hyperhidrosis (armpits, hands, and feet) affects approximately 4.8% of the US population (Doolittle, 2016[1]) and is believed to be caused by an overactive cholinergic response of the sweat glands. Current therapies have limitation in their efficacy, significant side effects, and/or are invasive and costly.

Oral and topical anticholinergic drugs, such as glycopyrrolate, have been used to treat hyperhidrosis, although they are not currently approved for this indication in the US. Their main limitations are systemic anticholinergic side effects (blurred vision, dizziness, dry mouth, constipation, urinary retention, and tachycardia).

"Soft-drugs" are designed to provide maximal therapeutic effect with minimal side effects. The synthesis of a soft-drug is achieved by starting with a known inactive or minimally active metabolite of a known active drug (e.g., glycopyrrolate). The inactive metabolite is then structurally modified to an active form that will undergo a predictable one-step transformation back to the inactive or less active metabolite *in vivo*. Thus, the soft-drug concept is based upon predictable metabolic deactivation by enzymatic and hydrolytic processes, which occur predominately in the systemic circulation.

Sofpironium bromide was designed as a structural analog of glycopyrrolate, a well-known, potent anticholinergic. The ester structure of sofpironium bromide allows for a rapid conversion via enzymatic and hydrolytic processes into a less active metabolite (carboxylic acid metabolite, referred to as BBI-4010). The predicted metabolite (BBI-4010) is highly polar and ionized at physiological pH, and thus is predicted to be subject to rapid elimination from the systemic circulation. This drug design is expected to result in the reduction of undesirable systemic anticholinergic effects while maintaining intended topical efficacy.

The initial nonclinical and clinical programs were conducted with a gel formulation consisting of sofpironium bromide dissolved in an anhydrous base of hydroxypropyl cellulose, hexylene glycol, citric acid anhydrous, dehydrated alcohol, and the novel excipient dimethiconol blend 20 (DB20), which was used in the formulation to improve the product's aesthetic properties. The DB20 gel formulation was evaluated in nonclinical studies with sofpironium bromide concentrations up to 20% and in clinical studies with sofpironium bromide concentrations of 0% (placebo), 5%, 10%, and 15% applied topically to the axillae or palms.

Although these studies demonstrated that the sofpironium bromide DB20 gel at these concentrations was safe and well tolerated, sofpironium bromide gel was reformulated by replacing DB20 with isopropyl myristate (IPM, a generally recognized as safe [GRAS] ingredient) due to concerns about physical instability of DB20 during process transfer and scale up. Please refer to the sofpironium bromide Investigator's Brochure for more information on DB20 and IPM gel formulations and their use in nonclinical and clinical studies to date. The IPM gel formulation will be used for all future clinical studies and commercialization. Unless otherwise indicated, "sofpironium bromide gel" refers to the IPM formulation. The DB20 and IPM formulation designations are used for clarity as needed.

In the current multicenter, randomized, open-label, Phase 3 long-term safety study, we are studying the long-term safety and tolerability of sofpironium bromide IPM gel, 5% and 15% when applied topically in subjects with axillary hyperhidrosis, over a 48-week period. Additionally, this study will evaluate the long-term effect of sofpironium bromide IPM gel, 5% and 15% on Investigator and patient-reported local tolerability assessments

and patient-reported subject satisfaction.

Nonclinical Studies

A comprehensive battery of pharmacology, safety pharmacology, 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 clinical route of administration.

Results of *in vitro* pharmacology evaluations have demonstrated high binding activity of sofpironium at all muscarinic receptors, and ex vivo anticholinergic activity was shown in a guinea pig model. Pharmacokinetic studies showed that sofpironium protein binding and distribution to blood cells was low, concentration-independent, and similar across animal species and human. Sofpironium distribution to tissues was wide, and distribution and elimination were independent of administration route following single subcutaneous (SC) or topical dosing. Placental transfer of 14C-sofpironium or its metabolites was low and transfer into the milk of lactating rats was observed. Extensive toxicologic evaluations demonstrated that sofpironium bromide gel was well tolerated locally and was not systemically toxic following administration by any route.

Sofpironium bromide was not mutagenic or clastogenic in a comprehensive battery of genotoxicity assays nor was it identified as a reproductive toxicant. Sofpironium bromide is currently under evaluation for carcinogenicity potential following dermal administration in mice and SC administration in rats. Sofpironium bromide gel was not identified as a dermal sensitizer. *In vitro*, sofpironium bromide gel, 20% demonstrated the potential to cause eye damage. Neither sofpironium bromide gel (DB20 and IPM) absorbed ultraviolet light between the 290 nm to 700 nm wavelengths and thus do not possess phototoxicity potential. Safety pharmacology studies did not identify any central nervous system, cardiovascular, or respiratory adverse effects.

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

Prior Human Experience

As of 31 December 2017, a total of 10 clinical studies, encompassing approximately 640 subject exposures, have been conducted with sofpironium bromide gel. Brief summaries are provided in the following paragraphs. Please refer to the sofpironium bromide Investigator's Brochure for more detailed descriptions and results.

Study BBI-4000-01 (ex-US)
This was a Phase 1, randomized, within-group controlled, double-blinded study of sofpironium bromide DB20 gel conducted in 28 healthy adult males. The study objective was to investigate skin irritability and safety of a single application of sofpironium bromide gel by patch test. Each subject received all of the following substances applied on the back, which were left on the subjects for 48 hours: 5%, 10%, and 15% sofpironium bromide DB20 gel; 0% sofpironium bromide DB20 gel (placebo); 0.5% sodium lauryl sulfate solution (positive-control); deionized water (negative-control); and patch test unit only.

Study BBI-4000-03 (ex-US)
This was a Phase 1, randomized, repeat-dose study of sofpironium bromide IPM gel conducted in 24 adults with primary axillary hyperhidrosis. The objective of this study was to investigate the pharmacokinetics (PK), local tolerability, safety, and efficacy of sofpironium bromide gel, 5%, 10%, or 15% when applied to the axillae in primary axillary hyperhidrosis. Subjects were randomized to either sofpironium bromide gel, 5%, 10%, or 15%, or vehicle gel (N=6 subjects per group), and applied the assigned product to the axillae once daily before bed for

28 days. The primary endpoint was assessment of PK measurements (plasma concentrations, urinary concentrations) of sofpironium and its metabolite, BBI-4010.

Study BBI-4000-04 (ex-US)
This was a Phase 2, randomized, vehicle-controlled, double-blinded study of sofpironium bromide gel conducted in 207 adults with primary axillary hyperhidrosis. The objective of this study was to investigate the efficacy, safety, and dose-relationship of sofpironium bromide gel in primary axillary hyperhidrosis. Subjects were randomized to 1 of 4 cohorts, either sofpironium bromide gel, 5% (n=52), 10% (n=51), 15% (n=52), or vehicle gel (placebo; n=52), and applied the assigned product to the axillae once daily, at bedtime, for 42 days. The primary efficacy objective was to assess the effect of sofpironium bromide gel, 5%, 10%, or 15% on sweat production. Measures associated with sweat production included direct measurement of gravimetric sweat production (GSP) and subjective assessments by the subjects (Hyperhidrosis Disease Severity Scale [HDSS], HDSM-Ax, DLQI).

Study BBI-4000-05 (ex-US)
This was a Phase 1, randomized, double-blinded, parallel-group, 14-day, repeat-dose study of sofpironium bromide IPM gel conducted in 24 adults with primary axillary hyperhidrosis. The objective of this study was to investigate the PK, local tolerability, and safety of 15% sofpironium bromide IPM1 gel vs. IPM2 gel when applied to the axillae in primary axillary hyperhidrosis patients once daily before bed for 14 days. IPM1 and IPM2 gel formulations differ in the citric acid concentration; IPM has 5.9g sofpironium bromide with 0.001% citric acid in a single 45ml pump, whereas IPM2 gel has 5.9g sofpironium bromide with 0.05% citric acid in a single 45ml pump. The primary endpoint was plasma concentration of sofpironium and its metabolite, BBI-4010.

Study BBI-4000-CL-101
This was a Phase 1, randomized, double-blinded, single-center study conducted in 24 subjects with primary axillary hyperhidrosis. The objective of this study was to investigate the local tolerability, safety, and effect of sofpironium bromide DB20 gel on sweat production (using GSP and HDSS). The study consisted of 2 consecutive cohorts, where Cohort 1 (N=6) established acceptable tolerability of sofpironium bromide DB20 gel, 5% (applied to one axilla) and vehicle gel to the other axilla prior to enrolling a separate group of subjects into Cohort 2. Subjects in Cohort 2 (N=18; 6 in each group) were randomized to receive sofpironium bromide DB20 gel, 5% or 10%, or vehicle gel (control) to both axillae once daily for 14 days. The primary efficacy endpoint was reduction in sweat production from baseline.

Study BBI-4000-CL-201
This was a Phase 2, multicenter, randomized, double-blinded, vehicle-controlled, parallel-group comparison study of 3 concentrations of sofpironium bromide DB20 gel (5%, 10%, and 15%) in 189 adults with primary axillary hyperhidrosis. The objectives of this study were to evaluate the safety and local tolerability of sofpironium bromide DB20 gel; the efficacy of sofpironium bromide DB20 gel as assessed by HDSS, HDSM-Ax, and GSP; the PK of sofpironium; and the psychometric performance of the HDSM-Ax as a measure of hyperhidrosis severity. Subjects applied the assigned study product topically to the axillae once a day for 28 days. In Part 1 of the study, 24 subjects were enrolled (6 in each arm). These subjects underwent PK blood draws and additional ECG analysis. After an interim safety and tolerability analysis, an additional 165 subjects were enrolled in Part 2 of the study.

Study BBI-4000-CL-202
This was a Phase 2, multicenter, randomized, double-blinded, vehicle-controlled, parallel-group study of sofpironium bromide DB20 gel, 15% conducted in 50 subjects with primary palmar hyperhidrosis. The objectives of this study were to assess the safety, local tolerability, and effect of sofpironium bromide DB20 gel, 15% on sweat production. This study was not powered to show statistically significant differences in the efficacy

endpoints. Subjects were randomized to either sofpironium bromide DB20 gel, 15% (n=25) or vehicle gel (placebo; n=25), and applied the assigned product to the palms of both hands once daily for 28 days. Measures associated with sweat production included GSP and subjective assessments by the subjects (HDSS, Hyperhidrosis Disease Severity Measure-Palm [HDSM-Palm], Palmar Hyperhidrosis Impact Scale [PHIS], and modified Dermatology Life Quality Index-Palm [DLQI-Palm]).

Study BBI-4000-CL-103
This was a Phase 1, single-center, 3-cohort, open-label, repeat-dose, PK, safety and tolerability study of sofpironium bromide IPM gel, 5%, sofpironium bromide IPM gel, 15% and sofpironium bromide DB20 gel, 15% formulations in 30 healthy subjects. The primary objective of this study was to evaluate the PK profile of sofpironium bromide and its metabolite, BBI-4010, following topical dosing. The secondary objective was to assess the safety and tolerability of topical dosing of sofpironium bromide. Subjects were randomized to 1 of 3 cohorts (n=10 each): 5% IPM gel, 15% IPM gel; and 15% DB20 gel; and applied the assigned drug to axillae once daily for 14 days.

Study BBI-4000-CL-203
This was a Phase 2, confirmatory, multicenter, randomized, double-blinded, vehicle-controlled, study comparing 3 different concentrations of sofpironium bromide IPM gel, 5%, 10%, and 15% with vehicle (placebo) in 227 adults with primary axillary hyperhidrosis. Subjects applied the assigned study product topically to the axillae once daily at bedtime for 42 consecutive days. The primary objectives of this study were to evaluate the effect of sofpironium bromide gel, 5%, 10%, and 15% on HDSM-Ax, and the safety and local tolerability of sofpironium bromide gel, 5%, 10%, and 15% when applied topically in subjects with axillary hyperhidrosis. Secondary objectives were to evaluate the effect of sofpironium bromide gel, 5%, 10%, and 15% on hyperhidrosis disease severity as it relates to GSP, HDSS, and DLQI. Subjects were randomized to 1 of 4 cohorts, either sofpironium bromide gel, 5% (n=57), 10% (n=57), 15% (n=56), or vehicle gel (placebo; n=57), and applied the assigned product to the axillae once daily, at bedtime, for 42 days.

Study BBI-4000-CL-102 (MUPK)
This was a Phase 1, open-label, non-randomized, repeat-dose study of sofpironium bromide gel, 15% under maximum-use conditions (3-fold higher clinical dose). The primary objective of this study was to evaluate the PK of sofpironium bromide gel, 15% and its major metabolite BBI-4010 following topical dosing. The secondary objectives of this study were to determine the safety, tolerability and efficacy of topical dosing of sofpironium bromide gel, 15% in subjects with axillary hyperhidrosis, as well as urine concentrations of sofpironium and its metabolite BBI-4010.

Overall Safety Conclusions
Sofpironium bromide was safe and well tolerated. All three, 5%, 10% and 15% dose groups have demonstrated comparable acceptability of safety and tolerability. TEAEs were dose-related with fewer subjects reporting AEs in the 5% dose group relative to 10% and 15% gel groups.

Consistent with the soft drug design, sofpironium bromide gel exhibited low incidence of anticholinergic AEs. The most common anticholinergic AE was dry mouth. All anticholinergic AEs were expected. Of note, the anticholinergic AEs were predominantly mild or moderate in severity and transient in duration. Of the application site AEs reported by Investigators (erythema, pain, dryness) and local tolerability signs reported by subjects (burning and itching), most were minimal in severity. All TEAEs resolved spontaneously with treatment discontinuation.

Overall Efficacy Conclusions
All three, 5%, 10% and 15% sofpironium bromide dose groups exhibited a larger absolute mean reduction in GSP from baseline to EOT compared to 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 dose groups were essentially equivalent in patient-reported outcome measures based on HDSM-Ax, HDSS, and DLQI. This suggests that each of the concentrations are efficacious. The response was seen as early as Day 8 and remained consistent throughout the applicable treatment period.

Overall Pharmacokinetics Conclusions
There was systemic exposure to both sofpironium and BBI-4010 analytes in the majority of subjects. Systemic exposure to sofpironium bromide appeared to increase in an approximately dose proportional manner between 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). The PK of sofpironium did not show accumulation. The plasma concentrations of BBI-4010 appear to be lower than those of sofpironium. Steady-state is reached by Day 14 and possibly Day 7. In general, preliminary PK analysis of the 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 0.050 ng/mL for sofpironium and BBI-4010, respectively.

Risk to Subjects
As an anticholinergic drug, topical administration of sofpironium bromide gel could be associated with signs or symptoms typical of a systemic anticholinergic effect such as dry mouth, blurred vision, dizziness, constipation, urinary retention, or tachycardia, among others. The previous sofpironium bromide exposure to humans has demonstrated a low incidence of these effects, which are generally mild in severity and transient. Of the approximately 640 total subjects exposed to sofpironium bromide, only ~2.0% subjects have discontinued from clinical studies due to anticholinergic effects.

2 STUDY DESIGN

This is a multicenter, randomized, open-label, Phase 3 long-term safety study of topically applied sofpironium bromide gel, 5% and 15% in subjects with axillary hyperhidrosis.

A maximum of 300 subjects, at approximately 30 clinical sites, will be enrolled to obtain approximately 150 subjects that have completed 12 months of dosing and clinical assessments.

Subjects will be randomized 1:2 to receive either sofpironium bromide gel, 5% or 15% (100 subjects dosed with 5% gel and 200 subjects dosed with 15% gel). Subjects will apply the investigational product once daily at bedtime, to their axillae for 12 months.

Vital signs and adverse events will be collected at each visit. Local tolerability assessments (including burning, itching, dryness, scaling, and erythema assessed using standardized scales) will be collected at each post-Screening visit. Blood and urine samples will be collected and analyzed at Screening and then Weeks 4, 12, 24, 36, and 48 for routine hematology, chemistry, and urinalysis parameters. Additionally, a urine pregnancy test (UPT) for females of child-bearing potential will be collected and analyzed at each visit except at Week 2 (Visit 3), Week 6 (Visit 5), and Week 52 (Visit 17). Patient-reported outcomes HDSM-Ax, PGI-S, PGI-C, and DLQI will be recorded during the study at predefined time points. HidroQoL will be recorded at baseline, Week 2, and Week 6; only the first 100 subjects enrolled in the study will complete this assessment.

A total of 17 scheduled visits will take place over approximately 52 weeks. 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 long-term safety, local tolerability, and efficacy of sofpironium bromide gel, 5% and 15% when applied topically in subjects with axillary hyperhidrosis.

3.1 Study Objectives

Primary:

To evaluate the long-term safety and local tolerability of sofpironium bromide gel, 5% and 15% when applied topically in subjects with axillary hyperhidrosis.

Secondary:

- To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on HDSM-Ax in subjects with axillary hyperhidrosis.
- To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on DLQI in subjects with axillary hyperhidrosis.

Other:

To evaluate the effect of topically applied sofpironium bromide gel, 5% and 15% on HidroQoL in subjects with axillary hyperhidrosis.

3.2 Study Assessments

Safety Measures:

The following safety assessment measures will be conducted to evaluate the long-term safety and local tolerability of sofpironium bromide gel, 5% and 15%:

- Adverse events
- Local tolerability assessments including burning, itching, dryness, scaling and erythema
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Laboratory tests (hematology, chemistry, and urinalysis) and pregnancy testing in FOCBP

Efficacy Assessments:

The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%:

- HDSM-Ax as measured by the subject
- 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 with each administration of the HDSM-Ax
† administered at Visit 10 (Week 24) and end of treatment Visit 16 (Week 48) only

Additionally, HidroQoL assessment will be conducted as an exploratory analysis, as measured by the subject (for subjects ≥17 years of age). This assessment will be performed at baseline, Visit 3 (Week 2), and Visit 5 (Week 6) for only the first 100 subjects enrolled in the study.

4 STUDY POPULATION

4.1 Number of Subjects

A maximum of 300 subjects, at approximately 30 clinical sites, will be randomized to receive either 5% or 15% sofpironium bromide gel in a 1:2 ratio to obtain approximately 150 subjects (50 subjects dosed for 48 weeks with 5% gel and 100 subjects dosed for 48 weeks with 15% gel) who have completed 12 months of dosing and clinical assessments.

4.2 Inclusion Criteria

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

1. Male or female subject ≥12 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 of 3-4 inclusive at both of the Screening visits (Visit 1) and Baseline Visit (Visit 2).
    b. Symptoms of axillary hyperhidrosis for ≥6 months' duration prior to Baseline Visit (Visit 2)
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 (if the subject reaches 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)* must agree to periodic pregnancy testing and use a medically acceptable method of contraception while receiving protocol-assigned product. Acceptable contraceptive methods include the following:
    a. Abstinence for the duration of the study, or where partner is sterile (e.g., vasectomy), is an acceptable form of contraception;
    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).

4.3 Exclusion Criteria

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

1. In the Investigators opinion, any skin or SC 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) within the specified timeframe for the treatment of axillary hyperhidrosis:
   - **a.** Botulinum toxin to the axillary area within 6 months of the Baseline Visit (Visit 2).
   - **b.** Axillary thermolysis, sympathectomy or surgical procedures of the axillary area at any time in the past.
   - **c.** 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 the Baseline Visit (Visit 2). However, if a subject has been on a stable dose (in the opinion of the PI) 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; they may be included. Doses of these agents should not be altered during the course of the study.
   - **d.** Any topical prescription treatment for hyperhidrosis within 15 days of Baseline Visit (Visit 2).
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 the Baseline Visit (Visit 2).
4. Use of potent oral inhibitors of cytochrome P450 CYP3A & CYP2D6 and transporter inhibitors (OCT2/MATE1/MATE2) within 14 days prior to the Baseline Visit (Visit 2). The use of topical antifungal medications is permitted if not applied in the treatment area. See Appendices 6 and 7.
5. Any oral or topical homeopathic or herbal treatment (i.e., alternative therapies such as sage tablets, chamomile, valerian root and St. John's Wort) within 7 days of the Baseline Visit (Visit 2).
6. Use of any cholinergic drug (e.g., bethanechol) within 15 days of the Baseline Visit (Visit 2).
7. Use of any anti-anxiety and/or anti-depressant, amphetamine product or drugs with known anticholinergic side effects is prohibited with the following exceptions:
   - **a.** If a subject 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; they may be included.
   - **b.** An amphetamine product may be allowed if the dose has been stable for ≥ 6 months without change in hyperhidrosis frequency or severity.
   - **c.** Drugs with known anticholinergic side effects (taken within the last 28 days) including dry mouth, 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 eCRF. The doses of these agents should not be altered during the course of the study.
8. Known cause of hyperhidrosis or known history of a condition that may cause hyperhidrosis (i.e., hyperhidrosis secondary to any known cause such hyperthyroidism, diabetes mellitus, medications, etc.).

9. Subjects with hyperhidrosis symptoms initiated or exacerbated with menopause.
10. Subjects with unstable type 1 or type 2 diabetes mellitus or thyroid disease, history of 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.
11. Known hypersensitivity to glycopyrrolate, anticholinergics, or any of the components of the topical formulation.
12. Subject is pregnant, lactating or is planning to become pregnant during the study.
13. Participating in a study or used an investigational drug or device within 28 days prior to the Baseline Visit (Visit 2).
14. Any major illness within 28 days before the Baseline Visit (Visit 2).
15. 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.
16. History or presence of supraventricular tachycardia, ventricular arrhythmias, atrial fibrillation or atrial flutter.
17. 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 hydroxylpropyl 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 and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44.

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 68°F to 77°F (20°C to 25°C) with excursion permitted between 59°F to 86°F (15°C to 30°C). 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 and 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, 5% or 15% to topically apply, once daily at bedtime, to each axilla using the supplied applicators for 48 consecutive weeks. 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 axillary dose application. Each full actuation of the pump corresponds to approximately 0.551 grams for the 5% and 0.576 grams for 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., Week 48, Visit 16). 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/dispensed at each of the Baseline Visit (Day1) and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 (Visits 4-15) for a total of 12 containers. Each of the 12 containers previously dispensed will be returned by the subject at the next respective visit, weighed and weight recorded per the unique bottle number. At the End of Treatment visit (Week 48), the subject will bring the 12th 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. Wash both hands and the plastic applicator thoroughly for about 2 minutes.
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 but should not shower, shave, or wash the underarm area for at least 8 hours after study product application. If the subject takes a shower, shaves or washes the underarm area at night then it should be at least 30 mins before study product application. 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 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.

6 CONCOMITANT MEDICATIONS/TREATMENTS

Information on concomitant medications/treatments (e.g., aspirin, Tylenol, birth control pills, IUD, vitamins) taken during study participation, or which may require a washout for study participation will be recorded. 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). 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 (I/E 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
- 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 (I/E criteria) including serotonergic agonists (or drugs that increase serotonin activity including SSRIs), beta-blockers, alpha-adrenergic agonist (clonidine), dopamine partial agonists, tricyclic antidepressants, anti-anxiety and/or other anti-depressant drugs, amphetamine products and drugs with known anticholinergic side effects.

Since no drug-drug interaction studies have been conducted to evaluate whether concomitant medications affect sofpironium bromide, potent inhibitors of CYP3A and, CYP2D6 and transporter inhibitors (OCT2/MATE1/ MATE2) should not be administered as specified in Sections 4.2 and 4.3 (I/E criteria): see Appendices 6 and 7.

7 PROCEDURES

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

Each subject will report for 17 distinct visits (over 52 weeks).

All Screening assessment results must be completed and reviewed prior to the Baseline 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 Baseline 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.

7.1 Time and Events Table

VISIT	1	2	3 – 6[1]	7 – 16[2]	17[3]
Time Point	**Screening (-31 to 0 Days)**	**Baseline (Day 1)**	**Weeks 2, 4, 6, 8 ±3 days**	**Q4 Weeks (Weeks 12 – 48) ±5 days**	**End of Study Week 52 ±5 days**
PROCEDURE					
Informed Consent	X				
Medical Hx, Demog	X				
I/E Criteria	X	X			
Randomization		X			
PE	X				X
Vitals (BP, HR, RR, Temp)	X	X	X	X	X
HDSM-Ax	X	X	X	X	X
PGI-S[4]	X	X	X	X	X
PGI-C[5]				X	
DLQI[6]		X	X	X	
HidroQoL[7]		X	X		
Local Tolerability[8]		X	X	X	X
Adverse Events[8]	X	X	X	X	X
UPT (FOCBP)[9]	X	X	X	X	
IP Dispensation/ Return/ Resupply[10]		X	X	X	
IP Weight[10]		X	X	X	
Compliance Training/Evaluation		X	X	X	X
Safety Labs (heme., chem., urine)[11]	X		X	X	
Conmeds	X	X	X	X	X

Abbreviations: BP = blood pressure; Chem. = chemistry; Conmeds = concomitant medications; DLQI = Dermatology Life Quality Index; FOCBP= females of child-bearing potential; HDSM-Ax = Hyperhidrosis Disease Severity Measure-Axillae; heme. = hematology; HR = heart rate; Hx = history; I/E = inclusion/exclusion; IP = investigational product; PE = physical examination; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; RR = respiratory rate; UPT = urine pregnancy test, urine = urinalysis.

[1]No more than 14±3 days may elapse between Visit 2 (Baseline) and Visit 3 (Week 2).

[2]No more than 28±5 days may elapse between each of Visits 7-16 (Weeks 12-48).

[3]The End of Study Visit may occur ±5 days of Week 52.

[4]Administered as Question #6 of HDSM-Ax at every assessment.
[5]Administered as Question #7 of HDSM-Ax at Week 24 and Week 48 visits.
[6]Administered at Baseline, Weeks 2, 6, 24, and 48.
[7]Administered at Baseline, Week 2, and Week 6; only the first 100 subjects enrolled in the study will complete this assessment.
[8] Investigator local tolerability assessments to be performed after the Subject local tolerability assessments.
[9] Performed at Screening, Baseline, and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
[10] Performed at Baseline and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.
[11] Performed at Screening and then Weeks 6, 24, and 48.

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 31 days prior to Visit 2 (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.
- Perform physical exam 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 (see Section 8.1.5).
- Subject to complete the HDSM-Ax assessment.
    - Six multi-part questions and PGI-S question to be completed by the subject prior to other assessments.
    - Refer to Appendix 1 (HDSM-Ax).
- Review the subject's health (AEs).
- 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 8.1.6).
- Review concomitant medications/treatments and assess for washouts.
- Schedule the subject to return for Visit 2 (Day 1; Baseline) after any washout has been completed; must be within 31 days of Visit 1 (Screening).

7.2.2 *Visit 2: Baseline (Day 1)*

Any washouts required for prohibited medications (See Section 4.3) must be completed prior to Visit 2 (Baseline).

The following activities will be conducted:

- Provided the subject has passed all I/E criteria, randomize the subject according to separate instruction. Note the subject's randomization number and the IP concentration the subject is assigned (5% or 15% sofpironium bromide gel).
- Collect vital signs (blood pressure, heart rate, respiratory rate, and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete the Hyperhidrosis Disease Severity Measure-Axillary assessment.

  - Subject to complete Patient Global Impression of Severity (PGI-S) at the end of the HDSM-Ax questionnaire.
- Subject to complete the DLQI questionnaire.
  - 10 questions to be completed by the subject.
  - Refer to Appendix 2.
- Subject to complete the HidroQoL questionnaire.
  - Only the first 100 subjects enrolled in the study to complete the questionnaire.
  - 18 questions to be completed by the subject.
  - Refer to Appendix 3.
- Perform local tolerability assessments (see Section 8.1.3).
- 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.
- Pull from inventory, a pump container of correct IP concentration recalling the earlier randomization step. Record the unique IP gel pump container number on the source document and in the appropriate electronic data capture (EDC) (or IRT) data field. Dispense study product container 1 to the subject as follows:
  - Write patient number and initials on the study product container label.
  - Prime the pump (5 actuations) and discard expressed gel.
  - Weigh the primed pump 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 patient 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 5).
  - Instruct subject to apply the first application of study medication at home the evening of Visit 2 (Baseline).
- Review concomitant medications/treatments.
- Schedule the subject to return for the next study visit.

7.2.3 *Visits 3-6 (Weeks 2, 4, 6, and 8) ±3 Days*

Visits 3, 4, 5 and 6 will occur as separate visits on Weeks 2, 4, 6, and 8 respectively, after the Baseline visit (Visit 2).

No more than 14±3 days may elapse between Visit 2 (Baseline) and Visit 3 (Week 2).

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 HDSM-Ax assessment.
  - Subject to complete PGI-S at the end of the HDSM-Ax questionnaire.
- Subject to complete the DLQI questionnaire at Visit 3 (Week 2) and Visit 5 (Week 6).
- Subject (only the first 100 subjects enrolled in the study) to complete HidroQoL at Visit 3 (Week 2) and Visit 5 (Week 6).
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).

- Perform UPT if applicable (FOCBP only) at Visit 4 (Week 4) and Visit 6 (Week 8). If positive, the subject shall be withdrawn from the study.
- Collect subject's previously dispensed study product container (1 of 12 at Visit 4 and 2 of 12 at Visit 6), weigh and record weight of container.
- Dispense study product container (2 of 12 at Visit 4; 3 of 12 at Visit 6) to the subject
    - Pull from inventory, a pump container of correct IP concentration recalling the randomization step (and which should match with the subject's returned product container). Record the unique IP gel pump container number on the source document and in the appropriate EDC (or IRT) data field.
    - Write patient number and initials on the study product container label.
    - Prime the pump (5 actuations) and discard expressed gel.
    - Weigh the primed pump and record in source prior to dispensing to the subject.
- Evaluate subject compliance:
    - Ask subjects if 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) at Visit 5 (Week 6) only.
- Review concomitant medications/treatments.
- Remind subject to bring their study medication product container to next visit.
- Schedule the subject to return for the next study visit.

7.2.4 *Visits 7-16 (Weeks 12-48) ±5 Days*

Visits 7 through 16 will occur as separate visits, every 4 weeks, on Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, after the Baseline Visit (Visit 2).

No more than 28±5 days may elapse between each of these visits.

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 HDSM-Ax assessment.
    - Subject to complete PGI-S at the end of the HDSM-Ax questionnaire.
    - Subject to complete PGI-C at the end of the HDSM-Ax questionnaire only at Visit 10 (Week 24) and Visit 16 EOT (Week 48).
- Subject to complete the DLQI questionnaire at Visit 10 (Week 24) and Visit 16 EOT (Week 48).
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Perform UPT if applicable (FOCBP only). If positive, the subject shall be withdrawn from the study.
- Collect subject's previously dispensed study product container, weigh and record weight of container.
- Dispense study product container (4 of 12 at Visit 7; 5 of 12 at Visit 8; 6 of 12 at Visit 9; 7 of 12 at Visit 10; 8 of 12 at Visit 11; 9 of 12 at Visit 12; 10 of 12 at Visit 13; 11 of 12 at Visit 14; and 12 of 12 at Visit 15; at Visit 16 only the subject's returned product container 12 will be weighed and recorded.)
    - At each dispensing, pull from inventory, a pump container of correct IP concentration recalling the randomization step (and which should match with the subject's returned product container).

Record the unique IP gel pump container number on the source document and in the appropriate EDC (or IRT) data field.
    - Write patient number and initials on the study product container label.
    - Prime the pump (5 actuations) and discard expressed gel.
    - Weigh the primed pump and record in source prior to dispensing to the subject.
- Evaluate subject compliance:
    - Ask subjects if 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) at Visit 10 (Week 24) and Visit 16 (Week 48).
- Review concomitant medications/treatments.
- Remind subject to bring their study medication to next visit.
- Schedule the subject to return for the next study visit.

7.2.5 *Visit 17 (End of Study) ±5 Days*

The following activities will be conducted:

- Perform physical exam including collection of height and weight.
- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for ≥2 minutes.
- Subject to complete HDSM-Ax assessment.
    - Subject to complete PGI-S at the end of the HDSM-Ax questionnaire.
- Perform local tolerability assessments.
- Review changes to the subject's health (AEs).
- Only if the subject did not return the study product container 12 at Visit 16, then weigh and record weight of container.
- 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 serious adverse event (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, identify the reason the subject withdrew consent should be documented with particular attention paid to whether an underlying AE is at cause.
- If for any reason per the Investigator's or the Sponsor's judgment, discontinuation is in the subject's best interest.
- If the subject becomes pregnant.

Subjects who discontinue the study prior to the completion of all treatment visits will be asked to complete the evaluations corresponding to Visit 16 (Week 48, 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.

- Adverse events
- Local tolerability assessments including burning, itching, dryness, scaling and erythema
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Laboratory tests (hematology, chemistry, and urinalysis) and pregnancy testing in FOCBP

8.1.1 *Physical Exam*

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 *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 8.1.3), 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?"

8.1.3 *Local Tolerability Assessments*

Local tolerability assessments (See Appendix 4) will be evaluated through assessment of selected local signs and symptoms at the drug-application site. Burning, itching, dryness, scaling and erythema will be assessed using standardized 5-point scales (0-Absent to 4-Severe). These assessments are to be performed for both axillae individually. Subject assessments (burning and itching) will be made prior to the Investigator assessments (dryness, scaling and erythema).

Subject Local Tolerability Assessments: Burning and itching for each axilla will be reviewed with the subject and assessed for the previous 24 hours using the standardized scales.

Investigator Local Tolerability Assessments: Dryness, scaling, and erythema for each axilla will be assessed by the Investigator using the standardized scales.

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

8.1.4 *Recommendations for Dose Interruption*

To manage AEs, the Investigator may consider interruption of treatment, and/or the use of concomitant therapy. Recommended concomitant therapy includes topically applied corticosteroids. Recommendations for dose interruption are described in the table below:

Recommended Dose Interruption

Dose Interruption	
First Dose Interruption	Hold treatment until the adverse event has resolved. Resume daily dosing.
Second Dose Interruption	Hold treatment until the adverse event has resolved. Decrease dosing to every other day.

Subjects who do not respond to a dose interruption or concomitant therapy can have the study drug withdrawn and be discontinued from the study.

8.1.5 *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.

8.1.6 *Clinical Laboratory Assessments*

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

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential*:
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils

Clinical Chemistry

BUN	Chloride	Alkaline phosphatase
Creatinine	AST (SGOT)	Total and direct bilirubin
Sodium	ALT (SGPT)	
Potassium	GGT	

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
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 in women ≥55 years of age).

All results will be reported and must be reviewed by the Investigator or designee. Abnormal results shall be assessed for clinical significance. Repeat lab 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.

8.1.7 *Subject Assessments*

Subjects must complete ALL self-assessments while at the clinic (e.g., HDSM-Ax, DLQI, PCI-S, PCI-C, HidroQoL) prior to assessments being made by the Investigator. Please see Appendix 1, Appendix 2, and Appendix 3 for a full description of these assessments. The HDSM-Ax, DLQI, PCI-S, PCI-C, and HidroQoL assessments will be collected electronically using a tablet device. Site personnel will be trained and a separate eCOA manual will be supplied.

8.2 Summary of Methods of Data Collection

This protocol will utilize validated 21 CFR Part 11 compliant 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 eCOA 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 and eCOA 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, 5% and 15%, as indicated in the Procedures Section 7.1:

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

8.4 Additional Efficacy Measure

The following efficacy assessment measure will be conducted as an exploratory analysis to evaluate sofpironium bromide gel, 5% and 15%, as indicated in the Procedures Section 7.1:

- HidroQoL as measured by the subject (for subjects ≥17 years of age); only the first 100 subjects enrolled in the study will complete this assessment

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 Sponsor (see Section 9.3.1). Contact information for the Sponsor's medical monitor is provided on the protocol covering page.

9.2 Adverse Events

9.2.1 *Definitions of Adverse Events*

According to the Code of Federal Regulations, 21 CFR Parts 312.32 and 320.32 (IND Safety Reporting, Applicability of requirements regarding an "Investigational New Drug Application"), 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 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 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 adverse event:

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

Abnormal laboratory values should not generally be recorded as an adverse event unless an intervention is required, the laboratory abnormality results in a serious adverse event, 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 adverse event 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 adverse event (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 dose of study drug will be recorded on the appropriate Adverse Events case report form (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 9.3.1).

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
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

Unknown

Not applicable

Other (specify on CRF)

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 Sponsor 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 Sponsor 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 patient at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The AE 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 patient's ability to carry out activities of daily living.
Congenital Anomaly or Birth Defect:	An adverse outcome in a child or fetus of a patient 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 patient 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 Sponsor 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 Sponsor within 24 hours of becoming aware of the new or follow-up information. The new or follow-up information should be faxed to the Sponsor at 1-866-666-7392 or emailed to safety@brickellbio.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 (21CFR 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 effective 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 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).

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 effective 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 Medical Monitor of this event, and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to the Medical Monitor by fax to 1-866-666-7392 or email at safety@brickellbiotech.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 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 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. All analyses will be performed separately for the 5% and 15% IP concentrations.

10 STATISTICAL PROCEDURES

A detailed statistical analysis plan 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

Subjects will be classified into the Safety, Intent-to-Treat (ITT), and Per-Protocol (PP) patient sets according to the following definitions.

Safety Patient Set

The Safety Patient Set will include all subjects randomized in the study who received study drug at least once. Subjects will be included in the treatment group based on the majority of actual treatment they received (even if not the treatment group to which they were randomized).

ITT Population

The ITT Patient Set will include all subjects who were randomized and dispensed study drug. Subjects will be included in the treatment group to which they were randomized, regardless of the treatment received.

PP Population

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

- Meets the inclusion/exclusion criteria
- Has not taken or applied any interfering concomitant medications.
- Completed the following visits:
    - Visit 1 (Screening) and the required data collection
    - Visit 2 (Baseline) and the required data collection
    - Visit 4 (Week 4), and the required data collection
    - Visit 7 (Week 12), and the required data collection
    - Visit 10 (Week 24), and the required data collection
    - Visit 16 (Week 48), and the required data collection
    - Visit 17 (Week 52), and the required data collection
- Required treatment received per randomization

10.2 Endpoints

Primary endpoints include evaluation of the long-term safety and local tolerability of 5% and 15% sofpironium bromide gel when applied topically in subjects with axillary hyperhidrosis. Assessment will include:

- Adverse events
- Local tolerability assessments including burning, itching, dryness, scaling, and erythema
- Vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- Laboratory tests (hematology, chemistry, and urinalysis) and pregnancy testing in FOCBP

Secondary endpoints - Efficacy:

Definitions

"Baseline" HDSM-Ax = Visit 2 (Week 2) assessment

"End of treatment" HDSM-Ax = Visit 16 (Week 48) assessment

Efficacy Endpoints

1. The proportion of subjects achieving ≥1-point improvement in HDSM-Ax from baseline to end of treatment
2. The proportion of subjects achieving ≥1.5-point improvement in HDSM-Ax from baseline to end of treatment
3. The proportion of subjects achieving ≥2-point improvement in HDSM-Ax from baseline to end of treatment
4. Change of HDSM-Ax from baseline to end of treatment as a continuous measure

Other Efficacy Endpoints

1. The proportion of subjects achieving ≥1-point improvement in the HDSM-Ax score from baseline to each of Visits 2-15 and 17 (Weeks 2-44 and Week 52)
2. The proportion of subjects achieving ≥1.5-point improvement in the HDSM-Ax score from baseline to each of Visits 2-15 and 17 (Weeks 2-44 and Week 52)
3. The proportion of subjects achieving ≥2-point improvement in the HDSM-Ax score from baseline to each of Visits 2-15 and 17 (Weeks 2-44 and Week 52)
4. Change in HDSM-Ax from baseline to each of Visits 2-15 and 17 (Weeks 2-44 and 52) as a continuous measure
5. DLQI from baseline to each of Visits 5, 10, and 16 (Weeks 2, 6, 24, and 48)
6. PGI-S summarized as frequency counts and percentages for each category (none, mild, moderate, severe, very severe) at each assessment, change from baseline as a 5x5 table with frequency counts and percentages at each post-baseline assessment
7. PGI-C summarized as frequency counts and percentages for each category (very much better, moderately better, a little better, no change, a little worse, moderately worse, very much worse) at Visits 10 and 16 (Weeks 24 and 48)

Exploratory Efficacy Endpoint

1. HidroQoL from baseline to each of Visits 3 and 5 (Weeks 2 and 6); only the first 100 subjects enrolled in the study will complete this assessment, and an interim analysis will be performed

10.3 Safety Analyses

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

At each post-screening visit, local tolerability (burning, itching, scaling, dryness, and erythema at either axilla) will be tabulated by severity. At each post-baseline visit, local tolerability will also be summarized as cumulative shift tables vs. baseline. Subject counts for each symptom will be cross tabulated by baseline severity and the maximum post baseline severity reported for either axilla up to the current visit.

Adverse events will be coded from the verbatim text into preferred term (PT) and primary system organ class (SOC) using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). At each post-baseline visit, treatment-emergent adverse events (TEAEs, i.e., AEs occurring during or after treatment initiation) will be summarized in the following tables: all reported AEs, all treatment-related AEs, all SAEs, and AEs leading to investigational product discontinuation. Three sets of the above tables will be produced at each visit: (a) for TEAEs reported at the current visit by those making the visit, (b) for cumulative TEAEs up to the current visit reported by those making the visit, and (c) for cumulative TEAEs up to the current visit reported by all enrolled patients (including those absent from the current visit). For each TEAE, a patient will appear at most once by the highest severity reported.

Laboratory parameters will be descriptively summarized (mean, SD, median, minimum, maximum) for values at each visit and for changes from screening at each subsequent visit. In addition, at each post-screening visit, parameter status (low, normal, high) will also be summarized as shift tables vs. screening status.

Vital signs will be descriptively summarized (mean, SD, median, minimum, maximum) for values at each visit and for changes from screening at each subsequent visit.

10.4 Efficacy Analyses

Descriptive summaries will be provided for all efficacy endpoints listed in Section 8.3 for each of the two dose groups. Mean, standard deviation, median, minimum and maximum will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables.

For HDSM-Ax, the mean of the items in sections No. 1, 2, and 3 (11 sub-items in total) will be used for analysis. The mean will be derived by taking the total score and dividing it by the number of questions answered. Subjects must answer ≥6 of the 11 sub-items to be evaluable for HDSM-Ax total score.

Missing data will not be imputed for any analyses.

10.5 Exploratory Analysis

Change in the HidroQoL from baseline to Week 2 and Week 6 will be assessed. Only the first 100 subjects enrolled in the study will complete this assessment, and an interim analysis will be performed.

10.6 Sample Size

A maximum of 300 subjects, at approximately 30 clinical sites, will be randomized to receive either sofpironium bromide gel, 5% or 15% in a 1:2 ratio to obtain approximately 150 subjects (50 subjects dosed with 5% gel and 100 subjects dosed with 15% gel) who have completed 48 weeks of dosing and 52 weeks of clinical assessments.

11 STUDY ADMINISTRATION PROCEDURES

11.1 Subject Entry Procedures

11.1.1 *Overview of Entry Procedures*

Subjects with hyperhidrosis as defined by the criteria 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 7-digit subject screening number, this number will be composed of a 1-digit study number (3), a 3-digit site number followed by a 3-digit sequentially assigned number stating at 001, at each site. For instance, the first subject from site 01 will have 3001001 as their assigned subject screening number; the subsequent subject from this site will have 3001002 as their assigned subject screening number. The first subject from site 02 will have 3002001 as their assigned subject screening number; the subsequent subject from this site will have 3002002 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.

After subjects qualify for the study (as determined by the Investigator at the Screening Visit), they will be scheduled to return for a Baseline Visit where they will be randomized to one of the two investigational product concentrations (5% or 15%), notified of the IP gel concentration they are assigned to, and their screening number becomes their post-randomization subject number. Each kit carton will contain a treatment plastic pump, which will be labeled with the IP drug concentration contained within and have a unique bottle number displayed on the label. A kit of the proper drug concentration 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 randomization schedule. The Investigator will document the randomization and kit numbers dispensed to the subject in the source, in the IRT system and on the CRF. The tear-off portion of the carton label from the outer carton will be removed along the label perforation and placed into the study subject source file. In the event a subject is randomized but is not dispensed study medication (e.g., deemed ineligible at Baseline, withdraws consent) the randomization number will not be reassigned; the subject will be considered an early termination and the kit shall be placed in quarantine in the site's inventory.

Up to 300 subjects will be randomized to receive either sofpironium bromide gel, 5% or 15% in a ratio of 1:2 (100 subjects dosed with 5% gel and 200 subjects dosed with 15% gel).

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 if 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 if they experienced any problems dispensing the investigational product.
- Subjects will be asked if they used any other products on their axillae.
- Site staff will review concomitant medication use since the previous visit and determine if 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 enrollment into the study. Subjects may be consented at the Screening Visit and up to 31 days before the Baseline visit.

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 Good Clinical Practice (GCP) regulations and guidelines, e.g., the International Conference on Harmonisation (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) is to be obtained from each subject prior to enrollment into the study, in accordance with the applicable privacy requirements (e.g., the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information; 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 excursion 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 prepped 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.

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.

14 APPENDICES

APPENDIX 1: HYPERHIDROSIS DISEASE SEVERITY MEASURE-AXILLARY© (HDSM-AX)

Hyperhidrosis Disease Severity Measure--Axillary©, Version 1.3

(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 <u>severity</u> of your <u>underarm</u> sweating <u>over the past week</u>.[**]**

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 <u>overall change</u> in your <u>underarm</u> sweating <u>since you started taking the study medication</u>. [†]

☐ 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 with each administration of the HDSM-Ax**

† Administered at the 24 Week and 48 Week (EOT) visits only

APPENDIX 2: 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	❒ ❒ ❒ ❒ ❒

DERMATOLOGY LIFE QUALITY INDEX-Axilla

7.	Over the last week, has your **underarm sweating** prevented you from **working** or **studying**?	A little Not at all 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 3: HYPERHIDROSIS QUALITY OF LIFE INDEX (HIDROQOL©); **FOR SUBJECTS ≥17 YEARS OF AGE**

Hyperhidrosis Quality of Life Index (HidroQoL)

The statements in this questionnaire relate to how your life has been affected **by your excessive sweating condition (hyperhidrosis) in the last seven days including today.**

Please choose one box for each statement. If a statement does not apply to you please choose 'No, not at all'.

Domain 1: Daily life activities

		Very much	A little	No, not at all
1.	My choice of clothing is affected	❒	❒	❒
2.	My physical activities are affected	❒	❒	❒
3.	My hobbies are affected	❒	❒	❒
4.	My work is affected	❒	❒	❒
5.	I worry about the additional activities in dealing with my condition	❒	❒	❒
6.	My holidays are affected (e.g., planning, activities)	❒	❒	❒

Domain 2: Psychosocial life

		Very much	A little	No, not at all
7.	I feel nervous	❒	❒	❒
8.	I feel embarrassed	❒	❒	❒
9.	I feel frustrated	❒	❒	❒
10.	I feel uncomfortable physically expressing affection (e.g., hugging)	❒	❒	❒
11.	I think about sweating	❒	❒	❒

12.	I worry about my future health	❒	❒	❒
13.	I worry about people's reactions	❒	❒	❒
14.	I worry about leaving sweat marks on things	❒	❒	❒
15.	I avoid meeting new people	❒	❒	❒
16.	I avoid public speaking (e.g., presentations)	❒	❒	❒
17.	My appearance is affected	❒	❒	❒
18.	My sex life is affected	❒	❒	❒

Domain 1 Score: _____ Domain 2 Score: _____ Total score ____ (out of 36)

Please check that you have answered all questions

Thank you!

APPENDIX 4: 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 e-CRFs 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): The severity of burning and itching of the axilla as reported by the Subject to the Investigator:

Score	Burning	Itching
0 = Absent	Normal, no discomfort	Normal, no discomfort
1 = Minimal	An awareness, but no discomfort	An awareness, but no discomfort
2 = Mild	Noticeable discomfort causing intermittent awareness	Noticeable discomfort causing intermittent awareness
3 = Moderate	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

Local tolerability (Investigator): The Investigator will grade the severity of dryness, scaling, and erythema on each axilla as observed:

Score	Dryness	Scaling	Erythema
0 = Absent	None	No scaling	No redness
1 = Minimal	Barely perceptible dryness by palpation with no accentuation of skin markings, skin desquamation (flakes), or fissure formation	Fine scaling, barely perceptible	Faint red or pink coloration, barely perceptible
2 = Mild	Easily perceptible dryness by palpation with accentuation of skin markings but no skin desquamation (flakes) or fissure formation	Slight scaling, noticeable only with light scratching	Light red or pink coloration
3 = Moderate	Easily noted dryness with accentuation of skin markings and skin desquamation (small flakes) but no fissure formation	Definitely noticeable scaling	Medium red coloration
4 = Severe	Easily noted dryness with accentuation of skin markings, skin desquamation (large flakes), and/or fissure formation	Extensive scaling	Beet red coloration

APPENDIX 5: 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. Wash both hands and the plastic applicator thoroughly for about 2 minutes.
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 but should not shower, shave, or wash the underarm area for at least 8 hours after study product application. If the subject takes a shower, shaves or washes the underarm area at night then it should be at least 30 mins before study product application. 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 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.

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.
- Do not shower, shave, or wash the underarm area 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 or practice the required 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).
- Use a T-shirt to sleep or similar pajama and avoid touching the underarm area.
- Do not apply any other product to the axillary area (including deodorant) for at least 8 hours after study product application.
- 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 2 (Baseline): Visits 4 (Week 4), Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16), Visit 9 (Week 20), Visit 10 (Week 24), Visit 11 (Week 28), Visit 12 (Week 32), Visit 13 (Week 36), Visit 14 (Week 40), Visit 15 (Week 44) and Visit 16 (Week 48).

APPENDIX 6: EXAMPLE POTENT INHIBITORS OF CYP3A AND CYP2D6

Example Potent Inhibitors of CYP3A		
apigenin	hydroxyzine	protease inhibitors
antipsychotics	interferon	ritonavir
candesartan	isoniazid	St. John's Wort (and other herbal supplements)
chloramphenicol	itraconazole	
chlorpheniramine	ketoconazole	
clarithromycin	methoxsalen	sulphaphenazole
cobicistat	mibefradil	telithromycin
cilexetil (cyclohexylcarbonate ester prodrug of candesartan)	miconazole	tripelennamine
	mifepristone	valproic acid
	mometasone furoate	voriconazole
diphenhydramine	montelukast	zafirlukast
felodipine	nefazodone	
gestodene	promethazine	

Example Potent Inhibitors of CYP2D6		
bupropion	fluoxetine	paroxetine
quinidine	terbinafine	

Also refer to FDA reference link "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2]

Prohibited medications (see Section 6.2)

Discontinue within 14 days of the Baseline Visit (Visit 2) for hyperhidrosis.

APPENDIX 7: EXAMPLE POTENT INHIBITORS OF OCT-2/MATE1/MATE2 TRANSPORTERS

Example Potent Inhibitors of OCT2		
Cimetidine		

Example Potent Inhibitors of MATE1/MATE2		
Cimetidine	Dolutegravir	Isavuconazole
Ranolazine	Trimethoprim	Vandetanib

Also refer to FDA reference link "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2]

Prohibited medications (see Section 6.2)

Discontinue within 14 days of the Baseline Visit (Visit 2) for hyperhidrosis.

APPENDIX 8: 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-303/01 on all pages Footer: Added the amendment date and "Confidential" to all pages

Change Number	Section # / Name	Details of Change
2	Title Page	Added the date of amendment
	Original Text	**VERSION**: Original March 7, 2018
	Revised Text	**ORIGINAL PROTOCOL:** March 7, 2018 **AMENDMENT 01:** May 15, 2018

Change Number	Section # / Name	Details of Change
3	SYNOPSIS, Study Objectives	Removed HidroQoL from the secondary endpoints and added it as an "other" endpoint, which will be completed by only the first 100 subjects enrolled in the study
	Original Text	Secondary: • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax©) in subjects with axillary hyperhidrosis. • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on the Hyperhidrosis Quality of Life Index (HidroQoL©) in subjects with axillary hyperhidrosis. • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on patient reported Dermatology Life Quality

		Index (DLQI) in subjects with axillary hyperhidrosis.
	Revised Text	Secondary: • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax©) in subjects with axillary hyperhidrosis. • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on patient reported Dermatology Life Quality Index (DLQI) in subjects with axillary hyperhidrosis. Other: • To evaluate the effect of topically applied sofpironium bromide gel, 5% and 15% on the Hyperhidrosis Quality of Life Index (HidroQoL©) in subjects with axillary hyperhidrosis. Only the first 100 subjects enrolled will complete this assessment.

Change Number	Section # / Name	Details of Change
4	SYNOPSIS, Study Design	Reordered study design to present safety measures followed by efficacy assessments. Also removed HidroQoL assessment from key efficacy assessments
	Original Text	Patient-reported outcomes: HDSM-Ax, HidroQoL, and DLQI 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 24 Week and 48 Week (EOT) visits. Vital signs, local tolerability assessments (including burning, itching, dryness, scaling and erythema assessed using standardized scales), and adverse events will be collected at each visit. Urine pregnancy tests (UPT) for FOCBP will be taken throughout the course of the study and blood and urine samples will be collected and analyzed at the Screening Visit and at Visit 5 (Week 6), Visit 10

		(Week 24), and Visit 16 (Week 48) for routine hematology, chemistry, and urinalysis parameters.
	Revised Text	Vital signs, local tolerability assessments (including burning, itching, dryness, scaling and erythema assessed using standardized scales), and adverse events will be collected at each visit. Urine pregnancy tests (UPT) for FOCBP will be taken throughout the course of the study and blood and urine samples will be collected and analyzed at the Screening Visit and at Visit 5 (Week 6), Visit 10 (Week 24), and Visit 16 (Week 48) for routine hematology, chemistry, and urinalysis parameters. Patient-reported outcomes: HDSM-Ax and DLQI 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 24 Week and 48 Week (EOT) visits. HidroQoL will be recording during the study at baseline, Visit 3 (Week 2), and Visit 5 (Week 6); only the first 100 subjects enrolled will complete this asessment.

Change Number	Section # / Name	Details of Change
5	SYNOPSIS, Safety Measures and Efficacy Assessments	Inverted order of Efficacy Assessments section and Safety Measures section to align with order presented elsewhere in the protocol

Change Number	Section # / Name	Details of Change
6	SYNOPSIS, Efficacy Assessments	Removed HidroQoL assessment from key efficacy assessments
	Original Text	**Efficacy Assessments** The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%: • HDSM-Ax as measured by the subject • HidroQoL as measured by the subject (for subjects ≥17 years of age) • DLQI as measured by the subject (for subjects ≥17 years of age)

		• Patient Global Impression Scales; Severity (PGI-S) and Change (PGI-C)
	Revised Text	**Efficacy Assessments** The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%: • HDSM-Ax as measured by the subject • DLQI as measured by the subject (for subjects ≥17 years of age) • Patient Global Impression Scales; Severity (PGI-S) and Change (PGI-C) The HidroQoL assessment will be conducted as an exploratory analysis, as measured by the subject (for subjects ≥17 years of age). This assessment will be completed by only the first 100 subjects enrolled in the study.

Change Number	Section # / Name	Details of Change
7	SYNOPSIS, Statistical Methods	Changed the sub-header "Safety Analysis" to "Safety Analyses", and sub-header "Efficacy Analysis" to "Efficacy Analyses"

Change Number	Section # / Name	Details of Change
8	SYNOPSIS, Statistical Methods	Amended statistical methods to move the HidroQoL assessment from the Efficacy Analyses section to a new Exploratory Analysis section; to update the schedule of HidroQoL; and to note only the first 100 subjects will complete this assessment
	Original Text	Change in the HidroQoL and DLQI from baseline to Week 2, Week 6, Week 24, and Week 48 (EOT).
	Revised Text	Change in the DLQI from baseline to Week 2, Week 6, Week 24, and Week 48 (EOT). **Exploratory Analysis** Change in the HidroQoL from baseline to Week 2 and Week 6 will be assessed. Only the first 100 subjects enrolled in the study will complete this assessment, and an interim analysis including descriptive statistics will be performed.

Change Number	Section # / Name	Details of Change
9	Section 2, Study Design	Reordered study design to present safety measures followed by efficacy assessments. Also updated to amend HidroQoL assessment schedule
	Original Text	Patient-reported outcomes HDSM-Ax, HidroQoL, DLQI, PGI-S, and PGI-C will be recorded during the study at predefined time points. Vital signs and adverse events will be collected at each visit. Local tolerability assessments (including burning, itching, dryness, scaling, and erythema assessed using standardized scales) will be collected at each post-Screening visit. Blood and urine samples will be collected and analyzed at Screening and then Weeks 4, 12, 24, 36, and 48 for routine hematology, chemistry, and urinalysis parameters. Additionally, a urine pregnancy test (UPT) for females of child-bearing potential will be collected and analyzed at each visit except at Week 2 (Visit 3), Week 6 (Visit 5), and Week 52 (Visit 17).
	Revised Text	Vital signs and adverse events will be collected at each visit. Local tolerability assessments (including burning, itching, dryness, scaling, and erythema assessed using standardized scales) will be collected at each post-Screening visit. Blood and urine samples will be collected and analyzed at Screening and then Weeks 4, 12, 24, 36, and 48 for routine hematology, chemistry, and urinalysis parameters. Additionally, a urine pregnancy test (UPT) for females of child-bearing potential will be collected and analyzed at each visit except at Week 2 (Visit 3), Week 6 (Visit 5), and Week 52 (Visit 17). Patient-reported outcomes HDSM-Ax, DLQI, PGI-S, and PGI-C will be recorded during the study at predefined time points. HidroQoL will be recorded at baseline, Week 2, and Week 6; only the first 100 subjects enrolled in the study will complete this assessment.

Change Number	Section # / Name	Details of Change
10	Section 3.1, Study Objectives	Removed the HidroQoL assessment from the secondary objectives and added it as an "other" objective
	Original Text	Secondary: • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax©) in subjects with axillary hyperhidrosis. • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on the Hyperhidrosis Quality of Life Index (HidroQoL©) in subjects with axillary hyperhidrosis. • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on patient reported Dermatology Life Quality Index (DLQI) in subjects with axillary hyperhidrosis.
	Revised Text	Secondary: • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax©) in subjects with axillary hyperhidrosis. • To evaluate the long-term effect of topically applied sofpironium bromide gel, 5% and 15% on patient reported Dermatology Life Quality Index (DLQI) in subjects with axillary hyperhidrosis. Other: • To evaluate the effect of topically applied sofpironium bromide gel, 5% and 15% on the Hyperhidrosis Quality of Life Index (HidroQoL©) in subjects with axillary hyperhidrosis.

Change Number	Section # / Name	Details of Change
11	Section 3.2, Study Assessments	Removed HidroQoL from the efficacy assessment, and added additional assessments section with HidroQoL
	Original Text	The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%: • HDSM-Ax as measured by the subject • HidroQoL as measured by the subject for subjects ≥17 years of age • 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 with each administration of the HDSM-Ax † administered at Visit 10 (Week 24) and end of treatment Visit 16 (Week 48) only
	Revised Text	***Efficacy Assessments:*** The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%: • HDSM-Ax as measured by the subject • 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 with each administration of the HDSM-Ax † administered at Visit 10 (Week 24) and end of treatment Visit 16 (Week 48) only Additionally, HidroQoL assessment will be conducted as an exploratory analysis, as measured by the subject (for subjects ≥17 years of age). This assessment will be performed at baseline, Visit 3 (Week 2), and Visit 5 (Week 6) for only the first 100 subjects enrolled in the study.

Change Number	Section # / Name	Details of Change
12	Section 7.1, Time and Events Table	Updated table/footnotes to present HidroQoL assessment after DLQI, and to reflect amended schedule of the HidroQoL assessment
	Original Text	[6]Administered at Baseline, Weeks 2, 6, 24, and 48. [7] Investigator local tolerability assessments to be performed after the Subject local tolerability assessments. [8] Performed at Screening, Baseline, and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. [9] Performed at Baseline and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. [10] Performed at Screening and then Weeks 6, 24, and 48.
	Revised Text	[6]Administered at Baseline, Weeks 2, 6, 24, and 48. [7]Administered at Baseline, Week 2, and Week 6; only the first 100 subjects enrolled in the study will complete this assessment. [8] Investigator local tolerability assessments to be performed after the Subject local tolerability assessments. [9] Performed at Screening, Baseline, and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. [10] Performed at Baseline and then Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. [11] Performed at Screening and then Weeks 6, 24, and 48.

Change Number	Section # / Name	Details of Change
13	Section 7.2.2, Visit 2 Baseline (Day 1)	Amended section to move HidroQoL after DLQI, to reflect reordered appendices, and to note HidroQoL will be completed only by the first 100 subjects enrolled in the study

	Original Text	• Subject to complete the HidroQoL questionnaire.
		  ○ 18 questions to be completed by the subject.
		  ○ Refer to Appendix 2.
		• Subject to complete the DLQI questionnaire.
		  ○ 10 questions to be completed by the subject.
		  ○ Refer to Appendix 3.

	Revised Text	• Subject to complete the DLQI questionnaire.
		  ○ 10 questions to be completed by the subject.
		  ○ Refer to Appendix 2.
		• Subject to complete the HidroQoL questionnaire.
		  ○ Only the first 100 subjects enrolled in the study to complete the questionnaire.
		  ○ 18 questions to be completed by the subject.
		  ○ Refer to Appendix 3.

Change Number	Section # / Name	Details of Change
14	Section 7.2.3, Visits 3-6 (Weeks 2, 4, 6, and 8) ±3 Days	Amended section to move HidroQoL after DLQI, to refect updated schedule of HidroQoL, and to note HidroQoL will be completed only by the first 100 subjects enrolled in the study
	Original Text	• Subject to complete HidroQoL at Visit 3 (Week 2) and Visit 5 (Week 6). • Subject to complete the DLQI questionnaire at Visit 3 (Week 2) and Visit 5 (Week 6).
	Revised Text	• Subject to complete the DLQI questionnaire at Visit 3 (Week 2) and Visit 5 (Week 6). • Subject (only the first 100 subjects enrolled in the study) to complete HidroQoL at Visit 3 (Week 2) and Visit 5 (Week 6).

Change Number	Section # / Name	Details of Change
15	Section 7.2.4, Visits 7-16 (Weeks 12-48) ±5 Days	Deleted: • Subject to complete HidroQoL at Visit 10 (Week 24) and Visit 16 EOT (Week 48).

Change Number	Section # / Name	Details of Change
16	Section 8.1.7, Subject Assessments	Amended section to list HidroQoL after other efficacy assessments, and to update links to inverted Appendices 2 and 3
	Original Text	HDSM-Ax, HidroQoL, DLQI, PCI-S, and PCI-C
	Revised Text	HDSM-Ax, DLQI, PCI-S, PCI-C, and HidroQoL

Change Number	Section # / Name	Details of Change
17	Section 8.3, Efficacy Measures	Amended section to list HidroQoL after other efficacy assessments, and to update links to inverted Appendices 2 and 3
	Original Text	The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%, as indicated in the Procedures Section 7.1: • HDSM-Ax as measured by the subject • HidroQoL as measured by the subject (for

		subjects ≥17 years of age) • DLQI as measured by the subject (for subjects ≥17 years of age) • Patient Global Impression Scales; Severity (PGI-S) and Change (PGI-C)
	Revised Text	The following assessment measures will be conducted to evaluate the long-term efficacy of sofpironium bromide gel, 5% and 15%, as indicated in the Procedures Section 7.1: • HDSM-Ax as measured by the subject • DLQI as measured by the subject (for subjects ≥17 years of age) • Patient Global Impression Scales; Severity (PGI-S) and Change (PGI-C)

Change Number	Section # / Name	Details of Change
18	8.4, Additional Efficacy Measure	Added new section 8.4 to include HidroQoL as an additional efficacy measure, as follows: The following efficacy assessment measure will be conducted as an exploratory analysis to evaluate sofpironium bromide gel, 5% and 15%, as indicated in the Procedures Section 7.1: • HidroQoL as measured by the subject (for subjects ≥17 years of age); only the first 100 subjects enrolled in the study will complete this assessment

Change Number	Section # / Name	Details of Change
19	10.2, Endpoints	Moved HidroQoL from "Other Efficacy Endpoints" to "Exploratory Efficacy Endpoint" and amended HidroQoL assessment schedule, as follows: Exploratory Efficacy Endpoint 1. HidroQoL from baseline to each of Visits 3 and 5 (Weeks 2 and 6); only the first 100 subjects enrolled in the study will complete this assessment, and an interim analysis will be performed

Change Number	Section # / Name	Details of Change
20	10.5, Exploratory Analysis	Added section 10.5 to include HidroQoL as an exploratory analysis, as follows: **Exploratory Analysis** Change in the HidroQoL from baseline to Week 2 and Week 6 will be assessed. Only the first 100 subjects enrolled in the study will complete this assessment, and an interim analysis will be performed.

Change Number	Section # / Name	Details of Change
21	10.6, Sample Size	Updated Sample Size section from 10.5 to 10.6 to reflect new section 10.5 added above

Change Number	Section # / Name	Details of Change
22	Appendix 1	Updated HDSM-Ax assessment form to reflect latest version (Version 1.3), with minimal changes in formatting and scale

Change Number	Section # / Name	Details of Change
23	Appendices 2 and 3	Inverted Appendices 2 and 3 to present DLQI questionnaire before HidroQoL questionnaire

Change Number	Section # / Name	Details of Change
24	Appendix 8	Added new Appendix 8 to detail changes made in AMENDMENT 01