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A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of 5%, 10% and 15% Topically Applied BBI-4000 (Sofpironium Bromide) Gel in Subjects with Axillary Hyperhidrosis

PROTOCOL NUMBER:	BBI-4000-CL-203
NAME OF INVESTIGATIONAL PRODUCT:	BBI-4000 (Sofpironium Bromide)
ORIGINAL PROTOCOL:	November 22, 2016
AMENDMENT 1	February 22, 2017
SPONSOR:	Brickell Biotech, Inc. 5777 Central Ave., Suite 102 Boulder, CO
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SPONSOR SIGNATORY:

2/23/2017

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

STUDY TITLE: A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and the Efficacy of 5%, 10% and 15% Topically Applied BBI-4000 (Sofpironium Bromide) Gel in Subjects with Axillary Hyperhidrosis

CLINICAL PHASE: Phase 2 (Confirmatory Study)

STUDY OBJECTIVES:
Primary:
1. To evaluate the effect of BBI-4000 5%, 10% and 15 % gel on hyperhidrosis disease severity measure when applied topically in subjects with axillary hyperhidrosis.
2. To evaluate the safety and local tolerability of BBI-4000 5%, 10% and 15% gel when applied topically in subjects with axillary hyperhidrosis.

Secondary:
1. To evaluate the effect of BBI-4000 5%, 10% and 15% gel on hyperhidrosis disease severity as it relates to sweat production, patient reported and quality of life self-assessments.

STUDY ASSESSMENTS:

Efficacy Assessments:

The following assessment measures will be conducted to evaluate the efficacy of BBI-4000 5%, 10% and 15% gel:

- Hyperhidrosis Disease Severity Measurement-Axillary (HDSM-Ax) as measured by the subject
- Gravimetrically measured sweat production (GSP) as measured by the investigator
- Hyperhidrosis Disease Severity Scale (HDSS) as measured by the subject
- Dermatology Life Quality Index (DLQI) as measured by the subject

Safety Measures:

The following safety assessment measures will be conducted:

- 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 females of child-bearing potential

STUDY RATIONALE:
This is a Phase 2 confirmatory, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study comparing a new formulation of BBI-4000 5%, 10% and 15% gel with vehicle (placebo) in subjects with axillary hyperhidrosis.

Minor modifications to the BBI-4000 Topical Gel formulation have been made to replace the novel excipient, Dimethiconol Blend 20 (DB20), with isopropyl myristate (IPM). IPM is a well-

characterized, compendial excipient commonly used in topical formulations; it is fully soluble in the formulation and thus overcomes the manufacturing issues previously encountered with DB20. Previous studies were conducted with the original formulation (i.e. DB20). This study will be conducted with the new (to-be-marketed) formulation containing isopropyl myristate at 2.5% (w/w). All other materials are common to both formulations and at the same concentrations.

The BBI-4000 5%, 10% and 15% gel concentrations proposed for this Phase 2 study are expected to be safe and tolerable dose levels considering:

- the safety and tolerability profile observed in the Phase 1 clinical study (BBI-4000-CL-01) with concentrations of BBI-4000 5%, 10% and 15%
- the safety and tolerability profile observed in the Phase 1 clinical study (BBI-4000-CL-101) with concentrations of BBI-4000 up to 10%
- the PK, safety and tolerability profile observed in the Phase 2 study (BBI-4000-CL-201) with doses of 5%, 10% and 15% of BBI-4000
- the safety and tolerability profile observed in the Phase 2 study (BBI-4000-CL-202) with doses of 15% of BBI-4000
- the PK, safety and tolerability profile observed in the Phase 1 study (BBI-4000-CL-103) with doses of 5% and 15% of BBI-4000
- tolerability observed in the minipig studies including concentrations up to 20%

The estimated maximum drug exposure for the subjects enrolled in this Phase 2 study will be approximately 2.5 mg/kg/day (i.e., 1.3 mL of 15% BBI-4000 gel/day in a 70-kg adult).

RISKS TO SUBJECTS:

As an anticholinergic drug, topical administration of BBI-4000 gel could be associated with local reactions such irritation, erythema, burning, desquamation (scaling), and itch; as well as signs or symptoms typical of a systemic anticholinergic effect such as dry mouth, pupil dilation, blurred vision, dizziness, constipation, urinary retention, increase in body temperature, tachycardia, among others. The previous BBI-4000 exposure to humans has demonstrated a low incidence of these effects which were mild in severity. One subject who received BBI-4000 15% gel applied to the axillae in the Phase 2b (Study BBI-4000-CL-201) and two subjects who received BBI-4000 5 % and 15% gel applied to the axillae in the Phase 1 (Study BBI-4000-CL-103) study withdrew from the study due to anticholinergic AEs; moderate blurred vision, headache, urinary hesitation, and application site dryness (BBI-4000 15% CL-201 study); moderate urinary retention, mild dry eyes and dry mouth (BBI-4000 5% CL-103 study); and mild lightheaded and nausea (BBI-4000 15% CL-103 study).

STUDY DESIGN:

A maximum of 220 subjects, at approximately 25 clinical sites, will be enrolled to obtain approximately 200 subjects that have completed dosing and critical assessments.

Subjects will be randomized to receive BBI-4000 5%, or 10%, or 15% gel, or vehicle gel (placebo) in a balanced ratio of 1:1:1:1.

Subjects will apply the investigational product (BBI-4000 5% or 10% or 15% gel or vehicle gel); once daily at bedtime, to both axilla for 42 consecutive days.

Gravimetric assessments and patient-reported outcomes HDSM-Ax, HDSS and DLQI will be recorded during the study at predefined time points. 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. A urine pregnancy test (UPT) for females of child-bearing potential and blood and urine samples will be collected and analyzed at the Screening Visit and at the End of Treatment Visit for routine hematology, chemistry, and urinalysis parameters.

A total of 14 scheduled visits will take place over approximately 12 to 16 weeks, depending on when the Baseline Visit (treatment) is scheduled after the four (4) screening period visits: initial screening, GSP1 and GSP2, and Rescreening GSP3.

INVESTIGATIONAL PRODUCT INFORMATION:

BBI-4000 (sofpironium bromide) Gel is a clear to slightly translucent colorless gel packaged in a white colored, capped, metered pump container. Two pumps are combined with 4 applicators to provide one kit to facilitate 42 days of dosing. The total gel volume in each pump container is 45 mL (~ 40 g). The gross weight of each full pump container dispensed at Baseline and Visit 8 (Day 22) is 74 to 80 grams.

BBI-4000 (sofpironium bromide) 5%, 10%, or 15% Gel is an anhydrous gel formulation containing the drug substance in an anhydrous gel base comprising hydroxylpropyl cellulose NF, hexylene glycol NF, isopropyl myristate NF, citric acid anhydrous USP, and alcohol dehydrated USP.

As previously noted, the drug product is provided in a kit containing two plastic metered pump containers each containing 45 mL of investigational product. Each drug pump container is sufficient for 21 days of dosing, as dispensed per protocol instructions. One pump actuation delivers ~ 0.67 mL of the gel formulation.

BBI-4000 vehicle (placebo) gel will be identical in appearance and constituents to BBI-4000 (sofpironium bromide) Gel but will not contain BBI-4000. The placebo formulation is provided in the same plastic metered pump containers with the same applicators to provide matching kits. The vehicle pump container contains 45 mL placebo product. Each vehicle pump container is sufficient for 21 days of dosing, as dispensed per protocol instructions. One pump actuation delivers ~ 0.67 mL of the placebo formulation.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC_{last}	Area Under the Curve last measurement
BBI	Brickell Biotech, Inc.
BPH	Benign Prostatic Hyperplasia
bpm	Beats per minute
C	Celsius
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DB20	Dimethiconol Blend 20
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
F	Fahrenheit
FDA	Food and Drug Administration
FOCBP	Female of Childbearing Potential
g	Grams
GCP	Good clinical practice
GSP	Gravimetric Sweat Production
HDSS	Hyperhidrosis Disease Severity Scale
HDSM-Ax	Hyperhidrosis Disease Severity Measure-Axillary
HIPAA	Health Insurance Portability and Accountability Act
hr	Hour
ICF	Informed consent form
ICH	International Conference on Harmonisation
I/E	Inclusion and Exclusion Criteria
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
L	Left
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
MMRM	Mixed Model Repeated Measures
NF	National formulary
ng	Nanogram
nM	Nanomolar
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient Reported Outcome
PT	Preferred term
R	Right
SAE	Serious Adverse Event
SC	Subcutaneous
SOC	System organ class
SSRI	Selective serotonin re-uptake inhibitors
T_{max}	Time of maximum plasma concentration
US	United States of America
UPT	Urine Pregnancy Test
USP	United States Pharmacopeia

1 BACKGROUND AND CLINICAL RATIONALE

BBI-4000 (sofpironium bromide) is a novel soft-anticholinergic ester analog of glycopyrrolate in development for the topical treatment of hyperhidrosis. BBI-4000 is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. BBI-4000 gel is expected to inhibit the action of acetylcholine in sweat glands thereby reducing the extent of sweating. Please refer to the BBI-4000 Investigator's Brochure for more information on BBI-4000.

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 population in the US (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 limitation is the 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 processes by hydrolysis and enzymes found predominately in the systemic circulation.

Based on these concepts, BBI-4000 was designed as a structural analog of glycopyrrolate, a well-known potent anticholinergic. The ester structure of BBI-4000 allows for a rapid conversion via enzymatic and hydrolytic processes into a noticeably 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 should be subject to rapid elimination from the systemic circulation. This drug design is expected to result in a reduction of the potential undesirable systemic anticholinergic effects while maintaining the intended topical anticholinergic effect.

In this bridging study, we are studying a new formulation of the BBI-4000 gel product against vehicle gel (placebo) group. The previously studied formulation included 2.5% of Dimethiconol Blend (DB20) as an excipient. Minor modifications to the BBI-4000 (Sofpironium Bromide) Gel formulation have been made to replace DB20 with isopropyl myristate (IPM). DB20 was included in the original formulation at a low concentration (i.e. 2.5% w/w) to reduce the tackiness of the formulation during drying after application. During process scale up, DB20 could not be physically stabilized in the formulation, so an alternative excipient was identified. IPM is a well-characterized, compendial excipient commonly used in topical formulations; it is fully soluble in the formulation and thus overcomes the manufacturing issues previously encountered with DB20. All other materials are common to both formulations at the same concentrations.

The drug product is an anhydrous, clear to slightly translucent colorless gel with the following constituents: BBI-4000 as active ingredient, hydroxypropyl cellulose as a gelling agent, hexylene

glycol as a humectant, isopropyl myristate to increase the aesthetic properties of the gel (i.e. skin conditioner/lubricant), citric acid for pH adjustment and ethanol as the anhydrous vehicle.

The in-vitro penetration and permeation data indicate that the IPM formulation should provide similar deposition and exposure of topically applied BBI-4000 as compared to the original formulation containing DB20. In nonclinical repeat-dose bridging studies in mice and minipigs, the BBI-4000 IPM gel containing IPM exhibited a comparable toxicity profile to that of the original formulation. Hence, the change in formulation is not anticipated to result in increased risk to subjects participating in this study.

Nonclinical investigations showed that BBI-4000 is able to induce dose-dependent pupil dilation when applied to rabbit eyes, demonstrating its local anticholinergic effect. The maximum mydriatic effect is comparable to glycopyrrolate but with a shorter duration, as expected by its structural design. In this model, glycopyrrolate maintains pupil dilation for an extended period (i.e., ≈ 50% of maximum mydriasis remained at Day 3 following a single instillation of 0.2% solution), indicative of its long-lasting anticholinergic effect. The effect of BBI-4000, although of shorter duration (i.e., ≈ 50% of maximum mydriasis remained at 24 hours post instillation of 1% solution), demonstrates sufficient local anticholinergic effect while minimizing the potential risk of long-lasting side effects.

Systemic administration of BBI-4000 did not adversely affect the central nervous system in a functional observational assessment in rats or in a respiratory function evaluation in dogs. As expected by virtue of its mechanism of action as an anticholinergic drug, intravenous (IV) bolus infusion of BBI-4000 in dogs resulted in temporary increases in heart rate.

BBI-4000 is extensively metabolized in human hepatocytes, and in animal and human liver microsomes. The primary metabolite, BBI-4010, is formed by ester hydrolysis. Additional metabolism studies, and excretion studies, are ongoing. The *in vitro* plasma protein binding of BBI-4000 and BBI-4010 is low and independent of concentration.

The **dermal and systemic toxicity** of BBI-4000 gel was also investigated in a battery of nonclinical studies in rats, minipigs, dogs, and guinea pigs.

Repeat-dose toxicity studies of BBI-4000 DB20 gel were conducted in mice for durations of up to 13-weeks. Daily dermal unoccluded administration of up to 20% BBI-4000 DB20 gel for 23 h/day at a maximum target dose of 400 mg/kg/day was well tolerated without systemic toxicity. There were no BBI-4000-related dermal observations, adverse effects on body weight, food consumption, hematology parameters or organ weights. Toxicokinetics showed high inter-individual variation in plasma BBI-4000 concentrations in both genders thus establishment of a clear dose-response relationship and accumulation with repeat-dosing were not feasible. Overall, systemic BBI-4000 C_{max} and AUC_{24} did consistently increase with increasing dose and females generally exhibited higher systemic exposure than males. BBI-4010 exposures were also highly variable, plasma increases were non-dose-proportional, females had lower BBI-4010 exposure than males, and there was evidence of accumulation. A NOAEL was not established due to the non-dose-related, and pharmacologically mediated, mortality.

In minipigs, daily repeat-dose dermal administration of up to 20% BBI-4000 DB20 gel at a maximum dose of 76 mg/kg/day has been evaluated for up to 26-weeks (a 39-week toxicity study is on-going). No mortality or systemic toxicity has been observed in any study. Unoccluded dermal dosing for 23 h/day was well tolerated without BBI-4000-related effects on clinical signs,

physical examination, food consumption, body weights, clinical pathology, ophthalmology, ECG waveforms or intervals, organ weights, macroscopic examination or histology. Dermal observations of minimal irritation at the dosing sites have been observed. In the completed 28-day study, a NOAEL for BBI-4000 DB20 gel was considered to be >76 mg/kg/day (20% gel to ~10% BSA) corresponding to Day 28 AUC values of 3.80 ng•hr/mL and 7.93 ng•hr/mL in males and females, respectively. Toxicokinetic evaluation is on-going in the 39-week study.

BBI-4000 was administered subcutaneously (SC) to rats for up to 26-weeks. This SC route was chosen following completion of a 2-week dermal PK study of BBI-4000 DB20 gel in rats in which dermal tolerance was shown to be limited. The incidence and severity of dose-related erythema desquamation, and eschar was considered to preclude long-term repeat dosing by the topical route in rats.

SC doses of 20 mg/kg/day and 10 mg/kg/day BBI-4000 were evaluated in 7-day, and 28-day studies, respectively. There was no mortality or systemic toxicity; a Maximal Tolerated Dose (MTD) of 5 mg/kg/day BBI-4000 (in 0.9% NaCl) was determined for extended repeat dosing based on local injection site reactions. In pivotal studies, non-dose-related pharmacologically mediated mortality occurred due to ingestion of bedding material and food which lodged in the pharynx. Clinical signs included retching, gasping, piloerection, somnolence and anticholinergic-related mydriasis. There were no consistent signs of injection site irritation. Dose-related decreases in body weight/body weight gain and slight decreases in food consumption were noted in both genders. Systemic BBI-4000 and BBI-4010 exposures, based on AUC_{24}, increased with increasing dose over the dose range of 0.5 to 5.0 mg/kg/day, and increases were generally greater than dose-proportional. Both analytes showed evidence of accumulation over 13-weeks and 26-weeks of repeat daily dosing. Based on the results of the SC injection studies, a NOAEL of 0.5 mg/kg/day, and an MTD of 5 mg/kg/day, were identified for SC administration to rats.

The reformulated BBI-4000 IPM gel was evaluated in bridging toxicity studies in mice and minipigs. No toxicologically significant differences were noted between formulations in either species. In mice, there was no mortality or systemic toxicity associated with 15-days of unoccluded 23 h/day exposures to BBI-4000 IPM gel. No dermal signs, drug-related clinical observations, effects on body weight, or toxicologically significant effects on food consumption were observed. As was observed with BBI-4000 DB20 gel, systemic exposure to BBI-4000 and BBI-4010 was highly variable. Systemic BBI-4000 C_{max} and AUC_{23} did not show a consistent increase with increasing dose over the target dose range 100 to 400 mg/kg/day (density corrected doses of 84, 171 and 354 mg/kg/day BBI-4000). BBI-4010 plasma exposure was also highly variable but increased approximately proportionally to dose. There was no obvious gender difference; accumulation was not determined. A NOAEL of 400 mg/kg/day BBI-4000 (20% IPM gel concentration) was established for both genders.

In minipigs, the reformulated 20% BBI-4000 IPM gel was compared to 20% BBI-4000 DB20 gel at 23 h/day unoccluded dose of 76 mg/kg/day for 28 consecutive days. There was no systemic toxicity, clinical observations, or adverse effects on body weights, food consumption or clinical pathology in BBI-4000 or vehicle treated minipigs for either formulation. Dermal irritation was limited to intermittent slight focal erythema which was similar between formulations and vehicles. Toxicokinetic evaluation showed that plasma BBI-4000 concentrations were variable in both dose groups; by Day 28, the mean combined gender $AUC_{0\text{-last}}$ of BBI-4000 was 2.8-fold higher, and C_{max} was approximately 4-fold higher, after topical application of the IPM formulation than after

exposure to the DB20 gel formulation. BBI-4010 $AUC_{0\text{-last}}$ and C_{max} were approximately 2.0-fold higher in the IPM group than the DB20 group.

BBI-4000 did not demonstrate sensitization potential in guinea pigs. Additionally, BBI-4000 gel does not absorb UV in the photoactivation range and is thus not a direct photochemical photosensitizer. BBI-4000 gel did show a potential to cause eye damage *in vitro*.

Results from in vitro and in vivo genotoxicity studies did not identify a mutagenic or clastogenic risk for BBI-4000. A dermal carcinogenicity study in mice evaluating BBI-4000 gel, and a carcinogenicity evaluation of subcutaneous BBI-4000 in rats are planned to start before the end of 2016.

Overall, Brickell has completed a comprehensive panel of nonclinical studies to characterize the toxicity and safety profile of BBI-4000, including in vitro and in vivo pharmacology studies (nonclinical efficacy); cardiovascular, respiratory and central nervous system safety pharmacology studies; absorption, protein binding, metabolism, and TK studies; repeat-dose toxicity, reproductive and genetic toxicity; sensitization and ocular irritation studies; and drug product formulation bridging toxicity studies. A 39-week chronic repeat-dose dermal toxicity study in minipigs is currently in progress (week 26 is complete). Additional pharmacology; absorption, distribution, metabolism, excretion and drug-drug interaction studies; and reproductive toxicity studies are on-going or are planned. Systemic and dermal carcinogenicity studies are under initiation

Prior Human Experience

As of 1 October 2016, 5 clinical studies have been conducted with BBI-4000 gel exposing 244 subjects to the active ingredient: two Phase 1 studies in healthy adults, Phase 1 and Phase 2 studies in adults with primary axillary hyperhidrosis, and a Phase 2 study in adults with primary palmar hyperhidrosis.

To date, the majority of the clinical program was conducted with a gel formulation consisting of BBI-4000 dissolved in an anhydrous base of hydroxypropyl cellulose, hexylene glycol, citric acid anhydrous, dehydrated alcohol, and the novel excipient Dimethiconol Blend 20 (DB20), used to improve the gel product's aesthetic properties. To address DB20 physical stability concerns during scale up, a reformulated gel was created that substitutes DB20 with isopropyl myristate (IPM, a common compendial excipient). The two gel formulations are quantitatively the same, with DB20 being replaced with IPM at the same concentration resulting with a gel of similar density. In nonclinical repeat dose bridging studies in mice and minipigs, the BBI 4000 IPM gel exhibited a comparable toxicity profile to that of the original DB20 formulation. The IPM gel was first clinically introduced in study BBI-4000-CL-103 (see below).

Study BBI-4000-01 (ex-US)
This was a Phase 1, randomized, within-group controlled, double-blind study of BBI-4000 DB20 gel conducted in 28 healthy adult males. The objective of this study was to investigate skin irritability and safety of a single application of BBI-4000 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% BBI-4000 DB20 gel; 0% BBI-4000 DB20 gel (placebo); 0.5% sodium lauryl sulfate solution (positive-control); deionized water (negative-control); and patch test unit only.

All subjects completed the study. Only a few subjects expressed weak skin reactions (International

Contact Dermatitis Research Group [ICDRG] grade 1) after application of BBI-4000 gel in a patch test, which were not judged as adverse events (AEs) by investigators. Further, BBI-4000 gel induced skin reactions compatible to those seen with purified water, the negative control. Dose-related reactions to BBI-4000 were not identified, and no systemic AEs were reported in subjects.

Study BBI-4000-CL-101
This was a Phase 1, randomized, double-blind, 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 BBI-4000 DB20 gel on sweat production (using gravimetric and Hyperhidrosis Disease Severity Scale [HDSS] methods). The study consisted of 2 consecutive cohorts, where Cohort 1 (N = 6) established acceptable tolerability of 5% BBI-4000 DB20 gel (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 5% BBI-4000 DB20 gel, 10% BBI-4000 DB20 gel, or vehicle gel (control) to both axillae once daily for 14 days.

All 24 subjects completed the study. Local tolerability assessments indicated that 5% and 10% BBI-4000 DB20 gel topically applied to the axilla region was well tolerated over the 14-day treatment period. Minimal to mild erythema, itching, burning, and dryness were reported during treatment, usually limited to only 1 study visit and resolved spontaneously. No AEs, SAEs or deaths were reported.

The primary endpoint of mean percent reduction from baseline in sweat production at Day 15 was 63.2% and 67.6% for subjects treated with 5% and 10% BBI-4000 DB20 gel, respectively (compared to 52.4% subjects treated with vehicle gel). Overall, the subjects receiving BBI-4000 experienced better efficacy outcomes. Specifically, 67% of subjects receiving BBI-4000 DB20 gel (5% and 10% groups combined) achieved a ≥ 2-point improvement in the HDSS in comparison to 33% of subjects who received vehicle; and 75% of subjects receiving BBI-4000 (5% and 10% groups combined) achieved ≥ 50% sweat reduction compared to 33% of subjects who received vehicle. While BBI-4000 10% appeared to have a greater effect than BBI-4000 5% DB20 gel with regard to several efficacy outcomes, a larger study was required to confirm this potential difference.

Study BBI-4000-CL-201
This was a Phase 2, multicenter, randomized, double-blind, vehicle-controlled, parallel group comparison study of 3 concentrations of BBI-4000 DB20 gel (i.e. 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 BBI-4000 DB20 gel; the effect of BBI-4000 DB20 gel as assessed by the HDSS and sweat production; the PK of BBI-4000; the effect of BBI-4000 gel as assessed by the Hyperhidrosis Disease Severity Measure-Axillary Scale (HDSM-Ax); and the psychometric performance of the HDSM-Ax as a measure of hyperhidrosis severity.

Subjects applied the assigned study product topically to the axillary area 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. In total, 189 subjects were enrolled (ITT

population) at 12 study sites. Among the ITT population, 93.7% completed the study. Reasons for early discontinuation included withdrawal by subject (n=6), loss to follow-up (n=5), and AE (n=1).

All concentrations of BBI-4000 gel were well tolerated locally. The incidence of local tolerability signs was low and generally similar among treatment groups; and most tolerability signs were minimal in severity, occurred bilaterally, and typically transient. The incidence of treatment-emergent adverse events (TEAEs) was relatively low (21.2%), with the lowest incidence in the vehicle group (13.0%) and the highest in the 15% gel group (29.2%). Most TEAEs were mild in severity (63.8%) and were considered to be possibly, probably, or definitely related to treatment (66.7%). The most common TEAEs included dry mouth (4.2%), vision blurred (3.7%), and application site pain (2.6%). Observed systemic TEAEs were consistent with known adverse effects of drugs of this class (i.e., anti-cholinergic activity). There were no reported SAEs or deaths.

Overall, treatment with BBI-4000 15% gel demonstrated a significant improvement in efficacy variables compared to the vehicle gel at Day 29 (end of therapy [EOT]), with less marked improvement at Day 42. For the primary endpoint (≥2-point improvement in HDSS at Day 29), there was a statistical difference (p=0.044) among the 4 groups, with the active treatment groups having directionally better outcomes compared to the vehicle group. In addition, a significantly (p=0.010) higher proportion of subjects in the 15% gel group (38.3%) had a ≥2-point improvement in HDSS at Day 29 compared with the vehicle group (12.2%). Improvement in efficacy variables in the 15% gel group was greater than that of the lower concentrations of BBI-4000 gel and the vehicle gel, with trends for larger improvement with increasing concentrations of BBI-4000 (i.e., dose-response) for some endpoints.

Systemic exposure of BBI-4000 and its metabolite, BBI-4010, was minimal following the first dose and after multiple doses of BBI-4000 gel, with higher plasma concentrations observed in the 15% gel group. After multiple doses of 5% or 10% gel, absorption of BBI-4000 remained low; PK parameters were calculable for a single 5% gel subject (mean C_{max}=0.4460 ng/mL, median T_{max}=1 hr) and for a single 10% gel subject (mean C_{max}=0.7860 ng/mL, median T_{max}=1 hr). After multiple doses of 15% gel, measurable BBI-4000 concentrations were observed on Days 8, 15, and 25. For BBI-4000 15% gel group, mean C_{max} was 1.831 ng/mL with a median T_{max} of approximately 3 hours and $AUC_{0\text{-last}}$ of 16.03 hr•ng/mL. After the first dose of BBI-4000, plasma concentrations of BBI-4010 were BLQ for all subjects, except one (15% gel). After multiple BBI-4000 doses, BBI-4010 C_{max} was 0.5038 ng/mL with a median T_{max} of approximately 4 hours and $AUC_{0\text{-last}}$ of 5.283 hr•ng/mL.

Study BBI-4000-CL-202

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

Subjects were randomized to either BBI-4000 15% gel (n=25) or vehicle gel (placebo; n=25), and applied the assigned product to the palms of both hands once daily for 28 days. Of the ITT population (N=50), 86.0% completed the study. Reasons for discontinuation included lost to

follow-up (n=2), non-compliance with study drug (n=1), withdrawal by subject (n=1), AE (n=1), and other (n=2).

BBI-4000 15% gel was well tolerated. The incidence of local tolerability signs was low, and most tolerability signs were minimal to mild in severity, occurred bilaterally, and typically transient. Burning and itching were somewhat more frequent in the 15% gel group than the vehicle gel group; dryness was most frequent in the 15% gel group, with fewer subjects having erythema in both groups. The incidence of TEAEs was relatively low (24.5%), with a higher incidence in the 15% gel group (33.3%) than in the vehicle group (16.0%). The majority of AEs were mild in severity. The most common TEAEs included dry mouth (8.3%) and mydriasis (8.3%). Observed systemic TEAEs were consistent with known adverse effects of drugs of this class (i.e., anti-cholinergic activity). There were no SAEs or deaths.

Measures associated with sweat production included direct measurement of sweat production (gravimetric assessments) by the investigator and subjective assessments by the subjects (HDSS, Hyperhidrosis Disease Severity Measure-Palm scale (HDSM-Palm), Palmar Hyperhidrosis Impact Scale [PHIS], and modified Dermatology Life Quality Index-Palm [DLQI-Palm]). The primary efficacy objective was to assess the effect of BBI-4000 15% gel on sweat production. Although there were no significant differences between 15% gel and vehicle gel groups in any of the efficacy measures, the reduction in sweat production measured gravimetrically across multiple time points was more evident in the 15% gel group, though this decrease was not maintained at Day 29.

Additional ad hoc analysis was conducted to investigate 4 different criteria for treatment success in the BBI-4000 15% gel and vehicle gel groups (ITT population). This analysis demonstrated a trend for efficacy of BBI-4000 15% gel compared to the vehicle gel.

Study BBI-4000-CL-103
This was a Phase 1, single-center, 3-cohort, open-label, repeat-dose, PK, safety and tolerability study of 5% BBI-4000 isopropyl myristate (IPM) gel, 15% BBI-4000 IPM gel, and 15% BBI-4000 Dimethiconol Blend 20 (DB20) gel formulations in 30 healthy subjects. The primary objective of this study was to evaluate the PK profile of BBI-4000 and its metabolite, BBI-4010, following topical dosing. The secondary objective was to assess the safety and tolerability of topical dosing of BBI-4000.

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. Of the ITT population (N=30), 93.3% completed the study. Reasons for discontinuation included AE (n=1) and loss of consent (n=1).

Overall, all BBI-4000 gel treatments were well tolerated, and reported AEs were mild to moderate. The incidence of TEAEs was relatively low, with a higher incidence in the 15% IPM gel group (n=26) compared to the other groups (5% IPM gel, n=11; 15% DB20 gel, n=9). A total of 46 AEs was reported by 15 subjects, and all but one of the reported AEs were mild in severity (moderate urinary retention). The observed systemic reactions were consistent with known adverse effects of drugs of this class (i.e., anti-cholinergic activity). There were no reported SAEs or deaths.

The lower limit of quantification (LLOQ) was 0.0500 ng/mL for BBI-4000 and 0.100 ng/mL for BBI-4010. Quantifiable concentrations of BBI-4000 and BBI-4010 were observed in all 3 dose cohorts, allowing for calculation of C_{max} and AUC_{0-t} parameters.

- For BBI-4000, at Day 14, the mean C_{max} value for 15% IPM gel (11.2 ng/mL) was approximately 5-fold greater than in 5% IPM gel (2.23 ng/mL) or 15% DB20 gel (2.39) ng/mL), both of which were comparable.
- AUC_{0-t} data support increased absorption of BBI-4000 with the IPM gel formulation. Day 14 AUC_{0-t} for 15% IPM gel formulation (119 hr.ng/mL) was approximately 4-fold greater than that of either 5% IPM gel (31.0 hr.ng/mL) or 15% DB20 gel (30.9 hr.ng/mL), which were comparable.
- Similar trends were seen for BBI-4010, with an approximate 3-fold increase in C_{max}, and over a 2-fold increase in AUC_{0-t} values, for 15% IPM gel as compared to either the 5% IPM or 15% DB20 gel formulations.

Both the C_{max} and AUC findings in this study corroborate similar findings from a previous bridging toxicity study in minipigs, where toxicokinetics showed that BBI-4000 and BBI-4010 plasma exposures were 2.8-fold and 2.0-fold higher, respectively, after topical application of a 20% BBI-4000 IPM gel formulation in comparison to a 20% BBI-4000 DB20 gel formulation.

Risks to Subjects

As an anticholinergic drug, topical administration of BBI-4000 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 BBI-4000 exposure to humans has demonstrated a low incidence of these effects and mild in severity. One subject who received BBI-4000 15% gel applied to the axillae in the Phase 2b (Study BBI-4000-CL-201) and two subjects who received BBI-4000 5% and 15% gel applied to the axillae in the Phase 1 (Study BBI-4000-CL-103) withdrew from the study due to anticholinergic AEs; moderate blurred vision, headache, urinary hesitation, and application site dryness (BBI-4000 15% CL-201 study); moderate urinary retention, mild dry eyes and dry mouth (BBI-4000 5% CL-103 study); and mild lightheaded and nausea (BBI-4000 15% CL-103 study).

2 STUDY DESIGN

This is an outpatient Phase 2 confirmatory, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study comparing BBI-4000 5%, 10% and 15% gel containing IPM with vehicle (placebo) in subjects with axillary hyperhidrosis.

A maximum of 220 subjects, at approximately 25 clinical sites, will be enrolled to obtain approximately 200 subjects that have completed dosing and critical assessments.

Subjects will be randomized to receive BBI-4000 5%, or 10%, or 15% gel, or vehicle (placebo) gel in a balanced ratio of 1:1:1:1.

Subjects will apply the investigational product (BBI-4000 5%, 10% and 15% gel or vehicle; approximately 50 subjects per cohort) once daily at bedtime, to their axillae for 42 consecutive days.

Patient-reported outcomes (HDSM-Ax, HDSS & DLQI) and Gravimetric assessments will be recorded during the study at predefined time points. 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.

A urine pregnancy test (UPT) in females of child-bearing potential; and blood and urine samples will be collected and analyzed at the Screening Visit and at the End of Treatment Visit for routine hematology, chemistry, and urinalysis parameters.

A total of 14 scheduled visits will take place over approximately 12 to 16 weeks, depending on when the Baseline Visit (treatment) is scheduled after, and including, four (4) screening period visits: initial screening, GSP1 and GSP2, and Rescreening GSP3.

3 STUDY OBJECTIVES AND ASSESSMENTS

The purpose of this Phase 2 study is to assess the efficacy, safety, and local tolerability of the topical formulation BBI-4000 5%, 10% and 15% gel in subjects with axillary hyperhidrosis.

3.1 Study Objectives

Primary:

- To evaluate the effect of BBI-4000 5%, 10% and 15 % gel on Hyperhidrosis Disease Severity Measure (HDSM-Ax) when applied topically in subjects with axillary hyperhidrosis.
- To evaluate the safety and local tolerability of BBI-4000 5%, 10% and 15% gel when applied topically in subjects with axillary hyperhidrosis.

Secondary:

- To evaluate the effect of BBI-4000 5%, 10% and 15% gel on hyperhidrosis disease severity as it relates to gravimetrically measured sweat production (GSP), patient reported Hyperhidrosis Disease Severity Score (HDSS) and Dermatology Quality of Life Index (DLQI) self-assessment.

3.2 Study Assessments

Efficacy Assessments:

The following assessment measures will be conducted to evaluate the efficacy of BBI-4000

- Hyperhidrosis Disease Severity Measurement-Axillary (HDSM-Ax) as measured by the subject
- Gravimetrically measured sweat production (GSP) by the investigator
- Hyperhidrosis Disease Severity Scale (HDSS) as measured by the subject
- Dermatology Life Quality Index (DLQI) as measured by the subject

Safety Measures:

The following safety assessment measures will be conducted:

- 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 females of child bearing potential

4 STUDY POPULATION

4.1 Number of Subjects

A maximum of 220 subjects will be enrolled at approximately 25 study sites to obtain approximately 200 subjects that have completed dosing and critical assessments.

4.2 Inclusion Criteria

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

1. Male or female subject ≥ 18 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 4) (see Appendix 3).
    b. Gravimetric test indicating a minimum of 50 mg of sweat production at rest in each axilla with a two-axilla combined total of at least 150 mg of sweat production in five (5) minutes (at room temperature, 20ºC to 25ºC (68ºF to 77ºF)) at Screening Visit 1 and at least one of Visits 2, 3 or 4.
    c. HDSS of 3 or 4 at both of the Screening visits (Visit 1 and 4) (see Appendix 2).
    d. Symptoms of axillary hyperhidrosis for at least 6 months' duration
3. The ability to understand and sign a written informed consent form (ICF), which must be obtained prior to any study-related procedures (including medication wash-out, if required) and treatment.
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 female of childbearing potential (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 less than 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 at least 2 months prior to screening, OR
    - Two forms of non-hormonal contraception, including intrauterine devices (at least 1 week status post placement), or properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents, etc.).

    ***** Female of childbearing potential for this study includes any female 18 years of age or older who has not undergone successful surgical sterilization (hysterectomy, bilateral

tubal ligation (at least six months prior to baseline) or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea greater than 12 consecutive months in women 55 years or older).

4.3 Exclusion Criteria

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

1. In the Investigators opinion, any skin or subcutaneous tissue conditions of the axilla(s), (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 9 months of GSP1 (Visit 2).
   b. Axillary thermolysis, sympathectomy or surgical procedures of the axillary area at any time in the past.

      Prior axillary laser hair removal is permitted if more than 7 days prior to GSP1 (Visit 2).
   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 30 days of GSP1 (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 30 days of GSP1 (Visit 2).
   e. Any over-the-counter topical antiperspirant/deodorant (applied directly to the axilla(s)) within 7 days of GSP1 (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, etc.) within 30 days of GSP1 (Visit 2).
4. Use of potent inhibitors of cytochrome P450 CYP3A and CYP2D6, (see Appendix 7) within 14 days prior to GSP1 (Visit 2). The use of topical antifungal medications is permitted if not applied in the treatment area.
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 15 days of GSP1 (Visit 2).
6. Use of any cholinergic drug (e.g. bethanechol) within 30 days of GSP1 (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 at least 6 months without change in hyperhidrosis frequency or severity.

c. Drugs with known anticholinergic side effects (taken within the last 30 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 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. Subject with hyperhidrosis symptoms initiated or exacerbated with their 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. Subjects with 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 or used an investigational drug or device within 30 days prior to GSP1 (Visit 2).
14. Any major illness within 30 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.

5 INVESTIGATIONAL PRODUCT (IP)

BBI-4000 (sofpironium bromide) Gel is a clear to slightly translucent colorless gel and is packaged in a white colored, metered pump container. Two pump containers are packaged in a carton with 4 applicators. The total gel volume in each container is 45 mL (~ 40 g). The gross weight of each full container at baseline is approximately 74 to 80 grams. BBI-4000 (sofpironium bromide) Gel is an anhydrous gel formulation containing the drug substance in a gel base comprising hydroxylpropyl cellulose NF, hexylene glycol NF, isopropyl myristate NF, citric acid anhydrous USP, and alcohol dehydrated USP.

Each pump container is sufficient for 21 days of dosing, per protocol instructions. One pump actuation delivers ~ 0.67 mL of the gel formulation.

BBI-4000 vehicle (placebo) gel will be identical in appearance and constituents to BBI-4000 (sofpironium bromide) Gel, but will not contain the active ingredient, BBI-4000. Two placebo pump containers are packaged in a carton with 4 applicators to match the active drug product kits.

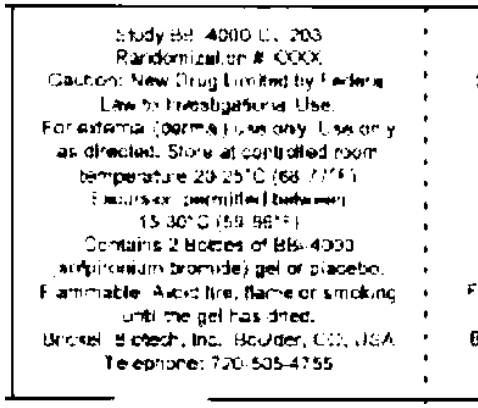
5.1 Methods for Masking/Blinding

The investigational materials will be packaged in identical-appearing pump containers in the same white cartons, each with four (4) applicators. The product will be identified as an investigational compound. The randomization number will be identified on each unit label. The investigational materials (i.e. each pump container and outer carton) will be labeled with panel labels.

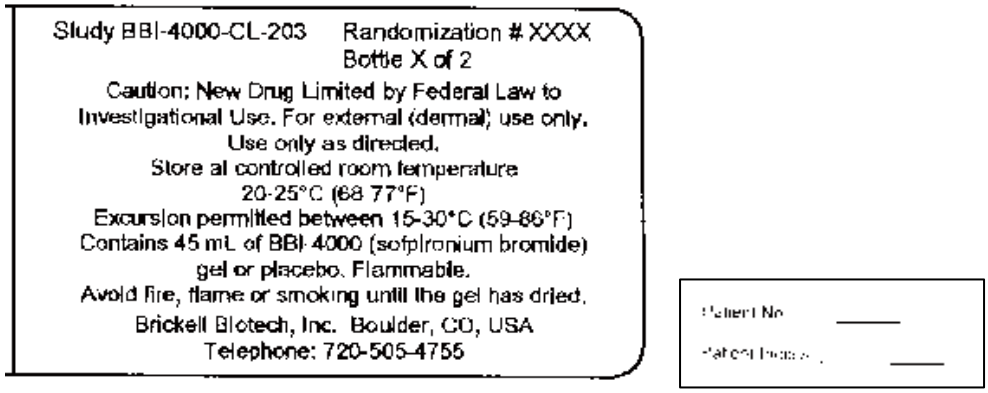
The outer carton will be labeled with a 2-part tear-off label which includes the blind-break panel. The first panel is permanently adhered to the carton and should not be removed. The tear-off portion with the blind-break panel will be separated along the label perforation and placed into the study subject source file. The blind-break panel will have a scratch-off area that can be removed, if needed, to reveal the specific product [i.e. active (corresponding strength) or placebo (vehicle)] provided to the study subject.

Each pump will have 2 labels: A one-panel label corresponding to the carton label and a second smaller label on which the subject number and initials should be recorded.

Example labels are provided below

1st Panel Adhered to Carton	Blind Break Panel to be Removed and Placed in Subject File
	

Panels Adhered to Pumps



5.2 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.

5.3 Instructions for Use and Administration of Investigational Product

The investigational product kit carton will be provided to each site and will include two individual plastic pump containers in one carton. Each carton will also contain 4 applicators. Each investigational plastic pump container will contain sufficient drug product for a 21-day treatment period.

Each carton will have a unique randomization number printed on the label and each of the two pump container labels will display the same unique randomization number.

Each subject will be randomized to receive BBI-4000 (sofpironium bromide) Gel 5%, or 10%, or 15%, or Vehicle to apply, once a day, to each axilla (1 pump per axillae) using the supplied applicators for 42 consecutive days.

Subjects will be instructed to apply the investigational product to each axilla with one full actuation of the pump for each dose application. Each actuation of the pump corresponds to approximately 0.56 grams (i.e., 0.67 mL) of investigational product.

The subject will apply all doses of investigational product at night, prior to going to bed with the supplied applicators. Subjects will apply their first dose of gel prior to bedtime the night of their Baseline Visit. The subject should be instructed to use their investigational product each night with the last application the night before attending the end of-treatment evaluation (i.e., Day 43 visit). Subjects should wash the applicator each night after dosing. Four applicators are provided in each kit to compensate for loss or damage during handling; it is not necessary to use all 4 applicators over the specified dosing interval.

To ensure accurate dosing, the Study Staff will be instructed to prime the pump container before dispensing to the subject by pressing the pump for three (3) sequential actuations and to discard to waste any dispensed gel from these 3 priming actuations.

The weight of the pump container with the cap on will be recorded after priming and will then be dispensed to the subject. Container 1 of 2 will be primed/weighed and then dispensed at the Baseline Visit along with the 4 applicators, and Container 2 of 2 will be primed/weighed/dispensed at Day 22 (Visit 8). Container 1 of 2 will be returned by the patient and weighed at Day 22 (Visit 8) and Container 2 of 2 will be returned by the patient and weighed at the End of Treatment Visit.

At Visit 8 (Day 22) and Visit 13 (Day 43, End of Treatment), the dispensed pump (Container 1 of 2 and 2 of 2 respectively) will be collected from the subject, weighed and compliance will be discussed and documented. Study subjects may return the applicators, or they may discard them after dosing is complete.

5.4 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 will be supplied to the Subject):

1. Expose the underarm areas and ensure they are dry. Don't wash the underarm areas prior to drying (no washing up to 30 minutes prior to drug application).

2. Carefully, by slowly applying pressure to the actuator with an index finger, place the gel of ONE full actuation onto the dome of the white plastic applicator.

3. Take the applicator using the three (3) middle fingers of the left hand in the plastic applicator hole and immediately apply study product to the right underarm area.

4. Distribute the product 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 over the treatment areas.

Important information:

- The subject should sleep in a T-shirt or similar loose fitting top 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 the subject should wait at least 30 mins before study product application. Ensure the underarm areas are dry before study product application.

- Subjects should not apply any other product to the axillary area (including sponsor supplied deodorant which should be used in the morning) 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 for about 2 minutes 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, flame or smoking during study product application and until the gel has dried. The subject should not expose the container to fire, flame or extreme heat.

On the day of a clinic study visit:

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

6 CONCOMITANT MEDICATIONS/TREATMENTS

Information on concomitant medications/treatments (e.g. aspirin, Tylenol, birth control pills, IUD, vitamins) taken during study participation, or which 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 topical product to their axillary area (e.g., antiperspirants, creams, etc.), with the exception of the use of the sponsor-supplied deodorant. The 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, the Medical Monitor and Brickell Biotech should be notified before a prohibited medication/treatment is administered.

Prior to the inclusion of a subject in the study, **as specified in Section 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, etc.).

- Any oral or topical homeopathic or herbal treatment (i.e. alternative therapies such as sage tablets, chamomile, valerian root and St. John's wart).
- Any topical product(s) including but not limited to cosmetics, prescription products, antiperspirants/deodorants or similar agents (e.g., Drysol, Xerac AC, Certain DRI, etc.) 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 Section 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 BBI-4000, potent inhibitors of CYP3A and, CYP2D6 should not be administered as specified in Section 4.3 and 4.2 (I/E criteria): see Appendix 7

7 PROCEDURES

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

Gravimetric assessments will be conducted between 7:00am - 11:00am.

Each subject will report for 14 distinct visits.

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

Subjects may be consented for up to 56 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.

Subjects who require a protocol-specified washout (see Section 4.3) must be consented at the time of stopping the medication. Washouts must be completed prior to Visit 2 (GSP 1) (i.e. within 35 days of the Screening Visit). In the event a subject does not satisfy the sweat production eligibility (Inclusion criteria 2b) at the Screening Visit, but is otherwise eligible to continue (i.e., satisfies all other eligibility requirements including HDSM-Ax and HDSS severity but may still require a washout), the Screening GSP may be retested once during the screening period at the discretion of the Investigator.

7.1 Time and Events Table

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
PROCEDURE	Screening			Rescreening	Baseline								End of Treatment	Follow-up
Gravimetric Timepoint		GSP 1	GSP 2	GSP 3							GSP 4	GSP 5	GSP 6	
Day (allowable window)	*Up to 35 days prior to GSP1*	*Up to 14 days from GSP1 to GSP3*			Day 1 (within 7 days of Rescreening)	Day 8 (± 2)	Day 15 (± 2)	Day 22 (± 2)	Day 29 (± 2)	Day 36 (± 2)	Day 41 (±2)	Day 42 (± 2)	Day 43 (± 2)	Day 57 (± 3)
Informed Consent	X													
Medical History, demographics	X			X										
Physical Exam				X										
Vital Signs (blood pressure, heart rate, respiratory rate and temperature)				X	X	X	X	X	X	X			X	X
I/E Criteria	X			X										
Gravimetric Assessments [a, b]	X	X	X	X		X	X	X	X	X	X	X	X	X
HDSM-Ax, HDSS	X			X		X	X	X	X	X	X	X	X	X
DLQI				X									X	
Local Tolerability Assessments [c]					X	X	X	X	X	X			X	X
Adverse Events [c]		X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization [d]				X										
Investigational Product [e] (IP) Dispensed / Returned					X[f]			X[f]					X	
IP Weight [g]					X			X					X	
Compliance Evaluation						X	X	X	X	X	X	X	X	
Safety Labs (hematology, chemistry, and urinalysis)	X												X	
UPT (females of childbearing potential only)[h]	X				X				X				X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a) Gravimetric assessments for all visits will be conducted from **7:00am-11:00am**.
b) One 5-minute gravimetric assessment will be conducted for each axilla. See section 4.2 (2b) for gravimetric assessment inclusion criteria.
c) Investigator assessments to be performed after the Subject assessments.
d) Randomization will take place only after the subject is qualified at the rescreening visit.
e) Order the investigational product only after the subject is qualified at the rescreening visit and randomized.
f) Pump 1 of 2 to be dispensed at Baseline (Visit 5). At Day 22 (Visit 8) Pump 2 of 2 to be primed and dispensed to patient. Written instructions for nightly dosing will be given to the subject. Subjects will apply their first dose of gel prior to bedtime the night of their Baseline visit. Instruct the subjects to return Pump 1 of 2 at Day 22 Visit 8 and Pump 2 of 2 at Day 43 (Visit 13, End of Treatment).
g) Pump container 1 of 2 will be weighed after priming at Baseline prior to dispensing to the subject and upon return at Day 22 (Visit 8). Pump container 2 of 2 will be weighed after priming at Day 22 (Visit 8) prior to dispensing to the subject and upon return at Day 43 (Visit 13, End of Treatment).
h) FOCBP for this study includes any female 18 years of age or older who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [at least six months prior to baseline] or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea greater than 12 consecutive months in women 55 years or older).

7.2 Visit-Specific Procedures

7.2.1 *Visit 1 (Screening)*

Written informed consent must be obtained prior to any study-related procedures. Potential subjects will be screened within 35 days prior to Visit 2 (GSP1) 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.
- Review concomitant medications/treatments and assess for washouts.
- Assess inclusion/exclusion criteria.
- Subject to complete the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) assessment.
    - Six multi-part questions to be completed by the subject prior to other assessments
    - Refer to Appendix 3
- Subject to complete the Hyperhidrosis Disease Severity Scale (HDSS) assessment
    - Refer to Appendix 2
- Perform Gravimetrically measured Sweat Production (GSP).
    - Gravimetric assessment must occur between **7:00 am-11:00 am.**
    - Refer to Appendix 1 for instructions and requirements of sample collection and handling
- Collect samples for laboratory assessments (hematology, chemistry and urinalysis).
- Perform Urine Pregnancy Testing (UPT) if applicable (FOCBP only). If positive, the subject shall be screen failed.
- Provide subject with the sponsor-provided non-antiperspirant deodorant. Resupply as needed throughout subject study participation.
- Schedule the subject to return for Visit 2 (GSP1) after any washout has been completed; must be within 35 days of Visit 1 (Screening).

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

- Retest must occur within the 35-days from Screening (Visit 1) and must occur prior to GSP1 (Visit 2).
- HDSM-Ax and HDSS must also be completed at the time of the Screening GSP retest.
- If subject does not meet inclusion based on GSP, HDSM-Ax and HDSS results at the time of the retest, the subject shall be screen failed and may not be rescreened.

Visits 2 through 4 will occur as separate visits between -1 to -day-14 after the initial screening visit (Visit 1).

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

- Showering in the morning is permissible.

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

7.2.2 *Visit 2 (GSP1) and Visit 3 (GSP2) – during Screening period*

Any washouts required for prohibited medications (See section 4.3) must be completed prior to Visit 2 (GSP1). GSP assessments 1, 2 and 3 must be conducted on separate days.

The following activities will be conducted:

- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**

7.2.3 *Visit 4 (Rescreening, GSP3) – during Screening period.*

No more than 14 days may elapse between Visit 2 (GSP1) and Visit 4 (Rescreening, GSP3).

The following activities will be conducted:

- Confirm subject medical history and demographics.
- Perform physical exam including collection of height and weight (see Section 8.2.1).
- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- Subject to complete the Dermatology life quality Index-Axilla (DLQI) questionnaire.
    - 10 questions to be completed by the subject.
    - Refer to Appendix 4
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Review inclusion/exclusion criteria to confirm eligibility
    - If subject eligibility is confirmed, contact Cu-Tech (CRO) to request Randomization Number assignment and shipment of subject's assigned product.
    - Is subject eligibility is not confirm, the subject shall be screen failed.
- Schedule the subject to return for Baseline within 2-7 days of Visit 4 (Rescreening).

7.2.4 *Visit 5 (Baseline, within 2-7 Days after Rescreening/Visit 4)*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Perform local tolerability assessments (see Section 8.2.6).

- Perform a UPT if applicable (FOCBP only). If positive, the subject shall be Early Terminated.
- Confirm the randomization number assigned to the subject corresponds to the kit received.
- Remove the tear-off unblinding panel from the kit carton and place in the subject's source records.
- Dispense study product container 1 of 2 to the subject:
    - Write patient number and initials on the study product container label.
    - Prime the pump (3 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 4 applicator
    - 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 6).
    - Instruct subject to apply the first application of study medication at home the evening of Visit 5 (Baseline).
    - Confirm the subject has adequate supply of the sponsor-provided non-antiperspirant deodorant and resupply as needed.
    - Subject should be reminded to bring their study medication with them to Visit 8 (Day 22).
- Schedule the subject to return for the next study visit.

7.2.5 *Visit 6 (Day 8 ±2) and Visit 7 (Day 15 ±2)*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- Perform local tolerability assessments.
- 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.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- Schedule the subject to return for the next study visit. At Visit 7 (Day 15) remind the subject to bring pump container 1 of 2 to Visit 8 (Day 22).

7.2.6 *Visit 8 (Day 22 ±2)*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.

- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- Perform local tolerability assessments.
- Collect subject's study product container 1 of 2, weigh and record weight of container.
- 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.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- Dispense study product container 2 of 2 to the subject
    - Write patient number and initials on the study product container label.
    - Prime the pump (3 actuations) and discard expressed gel.
    - Weigh the primed pump and record in source prior to dispensing to the subject.
- Remind subject to bring their study medication at Visit 13 (Day 43).
- Confirm the subject has adequate supply of the sponsor-provided non-antiperspirant deodorant and resupply as needed.
- Schedule the subject to return for the next study visit.

7.2.7 *Visit 9 (Day 29 ±2)*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- Perform local tolerability assessments.
- Perform a UPT if applicable (FOCBP only). If positive, the subject shall be Early Terminated.
- Evaluate subject compliance:
    - Ask subjects if they applied the study product to the right and left axilla each evening as directed confirm reason for any missed doses.
    - Verbally confirm application process.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- Confirm the subject has adequate supply of the sponsor-provided non-antiperspirant deodorant and resupply as needed.
- Schedule the subject to return for the next study visit.

7.2.8 *Visit 10 (Day 36 ±2)*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- Perform local tolerability assessments.
- 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. .
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- Confirm the subject has adequate supply of the sponsor-provided non-antiperspirant deodorant and resupply as needed.
- Schedule the subject to return for the next study visit.

7.2.9 *Visit 11 (Day 41 ±2, GSP4) and Visit 12 (Day 42 ±2, GSP5)*

The following activities will be conducted:

- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- 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.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am**.
- Confirm the subject has adequate supply of the sponsor-provided non-antiperspirant deodorant and resupply as needed.
- Schedule the subject to return for the next study visit. Remind the subject to bring pump container 2 of 2 to Visit 13 (Day 43).

7.2.10 *Visit 13 (Day 43 ±2, GSP6) / End of Treatment*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.

- Subject to complete the DLQI questionnaire.
- Perform local tolerability assessments.
- Perform a UPT if applicable (FOCBP only). If positive, the subject shall be Early Terminated.
- Collect samples for laboratory assessments (hematology, chemistry and urinalysis).
- Collect subject's study product container 2 of 2, weigh and record weight of container.
- 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.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- Confirm the subject has adequate supply of the sponsor-provided non-antiperspirant deodorant and resupply as needed.
- Schedule the subject to return for the next study visit.

7.2.11 *Visit 14 (Day 57 ±3) / 2 Week Follow-up / End of Study*

The following activities will be conducted:

- Collect vital signs (blood pressure, heart rate, respiratory rate and temperature) after subject has been seated for at least 2 minutes.
- Review changes to the subject's health (adverse events) and usage of concomitant medications/treatments.
- Subject to complete HDSM-Ax assessment.
- Subject to complete HDSS assessment.
- Perform local tolerability assessments.
- Perform GSP; gravimetric assessment must occur between **7:00 am-11:00 am.**
- 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 them 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 test investigational product.
- An exclusion criterion becomes apparent at any time during the study; contact the sponsor or medical monitor to discuss prior to discontinuing subject participation.
- The subject is not compliant with the study procedures; contact the sponsor or medical monitor to discuss prior to discontinuing subject participation.
- The subject voluntarily withdraws from the study. When possible, document the reason the subject withdrew consent.
- If for any reason per the Investigator's or Brickell'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 13 (Day 43, End of Treatment). The sponsor will be notified of early discontinuation as soon as possible during the study.

8 RESPONSE MEASURES AND SUMMARY OF DATA COLLECTION METHODS

8.1 Efficacy Measures

The following assessment measures will be conducted to evaluate the efficacy of BBI-4000 as indicated in the Procedures Section 7.1:

- Hyperhidrosis Disease Severity Measurement-Axillary (HDSM-Ax) as measured by the subject
- Hyperhidrosis Disease Severity Scale (HDSS) as measured by the subject
- Dermatology Life Quality Index (DLQI) as measured by the subject
- Gravimetrically measured sweat production (GSP) as measured by the investigator

Subjects must complete self-assessments prior to assessments being made by the investigator. Please see Appendices 1, 2, 3 and 4 for a full description of these assessments.

8.2 Safety Measures

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

8.2.1 *Physical Exam*

An abbreviated physical examination will be conducted at Rescreening (Visit 4) and 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.

8.2.2 *Vital Signs*

Subjects should be seated for at least 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.

8.2.3 *Clinical Laboratory Assessments*

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

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
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 18 years of age or older who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation (at least six months prior to baseline) or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea greater than 12 consecutive months in women 55 years or older).

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.

8.2.4 *Adverse Events*

Adverse events (See section 9) will be collected for all untoward medical occurrences in a subject entered into this clinical trial (e.g. signed consent) whether or not a pharmaceutical product has been administered. Any event, including local tolerability assessments (see Section 8.2.6) that

requires specific treatment, results in interruption of treatment, or results in discontinuation of the subject from the study will also be reported as Adverse Events.

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?"

8.2.5 *Subject Assessments*

Subjects must complete ALL self-assessments while at the clinic (e.g. HDSS, HDSM-Ax, DLQI) prior to assessments being made by the Investigator. Please see Appendices 2, 3, and 4 for a full description of these assessments.

8.2.6 *Local Tolerability Assessments*

Local tolerability assessments (See Appendix 5) 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.

8.3 Summary of Methods of Data Collection

This protocol will utilize validated 21CFR Part 11 compliant electronic data capture (EDC) software to collect CRF data. The investigator must ensure that data are properly recorded on each subject's eCRFs and related documents. When changes or corrections are made in the eCRF, the EDC system 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. 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.

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

9.1 Safety Assessments

Throughout the study, subjects will be monitored for signs and symptoms of AEs. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. This definition includes the worsening of a pre-existing condition, the development of investigational product dependency, and suspected investigational product-drug interactions.

Adverse events will be collected for all untoward medical occurrences in a subject entered into this clinical trial (as defined by the study protocol) whether or not a pharmaceutical product has been administered.

An *SAE* is an AE that meets one or more of the following criteria:

- Results in death (including reports of death with no specific AE identified, i.e., "death only" reports)
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not fall into one of the above categories but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes above

An *Unexpected AE* is any treatment-related AE that is not identified in nature, severity, or frequency in current literature on the test product (i.e., Investigators Brochure).

9.1.1 *Method of Detecting AEs and SAEs*

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?"

9.2 Reporting Requirements

9.2.1 *Serious and/or Unexpected Adverse Events*

Any serious or investigational product-related unexpected AE occurring in this study must be reported to the Medical Monitor/Brickell Biotech immediately upon awareness of the event per the following:

A SAE form must be completed by the investigator and **faxed to 973-331-1622 or email at wcunningham@cu-tech.com**. At the time of the initial report the following information should be provided at a minimum: subject identifiers, adverse event description, event status and severity, onset date, date the Investigator learned of the event, criteria for classification of the event as serious, disposition of the subject and Investigator assessment of the association between the event and study drug.

The investigator will keep the original of this SAE form on file at the study site. When the Investigator becomes aware of significant new information regarding an ongoing serious adverse event, a follow-up report should be promptly **faxed to 973-331-1622 or email at wcunningham@cu-tech.com**. When the investigator determines that there is no more information likely to be available, a final report should be provided.

9.2.2 *Adverse Event Reporting*

All AEs, including SAEs and treatment-related unexpected AEs, must be recorded by the investigator on the standard AE form. The investigator will be required to describe the AE, onset and stop date, severity, the course of action taken, if any, relationship to the study drug as well as any pertinent data necessary to allow a complete evaluation of the AE. For SAEs, an additional report must be completed (this form will be provided in the Investigator Site Binder).

A clinical determination of the intensity of an AE will be completed using the following definitions as guidelines:

Mild:	Awareness of sign or symptom, but easily tolerated
Moderate:	Discomfort enough to cause interference with usual activity
Severe:	Incapacitating with inability to work or do usual activity

The investigator must determine the relationship of the AE to the test article according to the following categories:

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.

9.2.3 *Pregnancy*

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 less than 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 at least 2 months prior to screening, OR
- Two forms of non-hormonal contraception, including intrauterine devices (at least 1-week status post placement), or properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents, etc.).

***** Females of childbearing potential for this study includes any female 18 years of age or older who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation (at least

six months prior to baseline) or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea greater than 12 consecutive months in women 55 years or older).

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.

9.2.3.1 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.

9.2.3.2 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 test article 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 or email as listed on the title page of the protocol. 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.

9.2.4 *Follow-up and Final Reports*

Subjects who have had a SAE must be followed clinically until all parameters, including laboratory values, have either returned to normal or are otherwise explained. If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

Subjects who report a pregnancy during the treatment phase of the study will be followed until pregnancy resolution and information regarding the health status of the infant will be collected.

9.3 Procedures for Unblinding of Investigational Product

The sponsor will break the blind for subjects only if the medical monitor in conjunction with the Sponsor deems that a conclusion regarding the progression of the study, as planned, cannot be made based on the blinded data.

In addition, when necessary for the safety and proper treatment of a subject, the investigator may unmask the subject's investigational product assignment to determine and institute appropriate care, and subsequently the subject will be discontinued from receiving treatment. When possible, the Sponsor should be notified prior to unmasking. To break blind, the investigator or a designee will scratch off the blind break area (see Section 5.1) on the label panel adhered to the subject record at the time of dispensing the investigational product. In the event of a premature breaking of the randomization code, the reason for breaking the code will be recorded in the subject's source documents.

10 STATISTICAL PROCEDURES

A detailed statistical analysis plan will be generated prior to the final database lock. Database lock will precede unblinding and 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 2 GSP 1, and the required GSP data collection
    - Visit 3 GSP 2, and the required GSP data collection
    - Visit 4 Re-screening GSP 3, and the required GSP data collection
    - Visit 11(GSP 4) Day 41 (± 2 days), and the required GSP data collection
    - Visit 12 (GSP 5) Day 42 (± 2 days), and the required GSP data collection

- Visit 13 (GSP 6) Day 43 (± 2 days), and the required GSP data collection

Subjects will be included in the treatment group based on the treatment received.

10.2 Endpoints

Generally, for statistical calculation of end of therapy change from baseline, baseline and end of therapy values are defined as follows.

HDSM-Ax and HDSS:

baseline value = average of two screening values, i.e. Visit 1 and Visit 4

end of therapy value = average of Days 41, 42, and 43 measurements, i.e. Visit 11, Visit 12, and Visit 13, respectively.

Gravimetric Sweat Production (both axilla combined):

baseline value = the median of GSP1, GSP2, and GSP3 measurements obtained on Visit 2, Visit 3, and Visit 4, respectively

end of therapy value = the median of GSP4, GSP5, and GSP6 measurements obtained on Visit 11, Visit 12, and Visit 13, respectively.

Primary efficacy endpoint will be defined as:

1. The proportion of subjects achieving at least a 1-point improvement in HDSM-Ax from baseline to end of therapy.
2. Change of HDSM-Ax from baseline to end of therapy as a continuous measure

Secondary efficacy endpoints will include the following.

1. The proportion of subjects achieving at least a 2-point improvement in HDSM-Ax from baseline to end of therapy.
2. The proportion of subjects achieving at least a 50% reduction in gravimetrically measured sweat production (both axilla combined) from baseline to end of therapy.
3. The absolute change from baseline in gravimetrically measured sweat production to end of therapy.
4. The percent change from baseline in gravimetrically measured sweat production to end of therapy.
5. The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax score and at least 50% reduction in gravimetrically measured sweat production from baseline to end of therapy.
6. The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax total score and at least 50% reduction in gravimetrically measured sweat production from baseline to end of therapy.
7. The proportion of subjects achieving at least a 2-point improvement in HDSS from baseline to end of therapy.

8. The proportion of subjects achieving at least a 1-point improvement in HDSS from baseline to end of therapy.

Other efficacy endpoints will include:

1. The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
2. Change in HDSM-Ax from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57 as a continuous measure
3. The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
4. The proportion of subjects achieving at least a 50% reduction in gravimetrically measured sweat production (both axilla combined) from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
5. Percent change from baseline in gravimetrically measured sweat production at Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
6. Absolute change from baseline in gravimetrically measured sweat production at Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
7. The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax score and at least 50% reduction in gravimetrically measured sweat production from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
8. The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax total score and at least 50% reduction in gravimetrically measured sweat production from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
9. The proportion of subjects achieving at least a 2-point improvement in HDSS from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
10. The proportion of subjects achieving at least a 1-point improvement in the HDSS on Days 8, 15, 22, 29, 36, 41, 42, 43, and 57.
11. Change in the modified dermatology life quality index (modified DLQI) from baseline to Day 43 (end of therapy), and Day 57.

10.3 Efficacy Analyses

Descriptive summaries will be provided for all efficacy endpoints by treatment groups at specified time points. Mean, standard deviation, median, minimum and maximum will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables. For continuous endpoints specified in 10.2, change from baseline will be similarly summarized.

Primary Efficacy Analyses

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

Change from baseline to end of therapy for the primary efficacy measure of HDSM-Ax will be analyzed both as a continuous measure and as a binary endpoint. As a continuous measure, the HDSM-Ax change scores will be compared between all active treatment groups and the vehicle group by an ANCOVA model adjusting for the baseline HDSM-Ax score. As a binary measure, i.e. achieving a 1-point improvement or not from baseline to end of therapy, a logistic regression will be performed with treatment assignment and baseline HDSM-Ax score as independent variables in the model. As a phase 2 study, a 1-sided $p<0.10$ in favor of an active treatment will be regarded as a positive sign for further investigation.

Missing data will not be imputed for the primary analyses. As sensitivity analyses, mixed model repeated measures (MMRM) analyses may be performed using all available HDSM-Ax change from baseline data on study days 8, 15, 22, 29, 36, and end of therapy.

Additional Efficacy Analyses

Analyses for secondary and other efficacy endpoints will be similar to the binary HDSM-Ax analysis described above. For gravimetric results analyzed as continuous measures, analyses assuming Normality for the data distribution (i.e. comparing means) and analyses using rank transformed data (i.e. comparing medians) will both be performed. All non-primary analyses will be based on available data only.

In parallel to the traditional statistical analysis, psychometric evaluation of the HDSM-Ax will be carried out to confirm the most appropriate HDSM-Ax scoring algorithm and to examine internal validity, construct validity (i.e., examinations of the magnitude of correlation between the HDSM-Ax total score (Items 1, 2, and 3) and key variables such as; items 4 and 5 of the HDSM-Ax, HDSS and gravimetrically measured sweat production), stability, reliability, ability to detect change, and interpretability of clinical trial results.

10.4 Safety Analyses

Safety variables are AEs, blood laboratory evaluations, UPTs (as required), local tolerability assessments and vital signs.

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). Treatment-emergent AEs will be summarized in the following tables: all reported AEs, all treatment-related AEs, all SAEs, and AEs leading to investigational product discontinuation. The number and percent of subjects reporting the AE at least once will be tabulated according to the highest severity reported.

Laboratory evaluations and UPTs parameters will be summarized.

Vital signs, including changes from baseline, will be summarized by descriptive statistical methods as previously described.

Local tolerability assessments will also be summarized similarly as the treatment related AEs.

10.5 Sample Size and Power Estimation

For the binary version of the primary endpoint, i.e. proportion of subjects achieving at least a 1-point improvement in HDSM-Ax from baseline to end of therapy, assume the true response rates

to be 75% for each BBI-4000 arm and 50% for vehicle control (based on prior data). With 100 evaluable subjects at a 1:1 ratio for each pairwise comparison between a BBI-4000 arm and the vehicle arm, i.e. 50 evaluable subjects per arm, the power is approximately 0.87 for observing a response rate difference in favor of BBI-4000 at a 1-sided $p<0.10$ level. To limit the study-wide false positive rate to 0.10, a gate-keeping hierarchical testing algorithm will be employed. That is, the BBI-4000 15% group will be compared to the vehicle first, if the result is favorable with a 1-sided $p<0.10$, then the BBI-4000 10% group will be compared to vehicle. Similarly, if the BBI-4000 10 % is favorable with a 1-sided $p<0.10$, then the BBI-4000 5% group will be compared to vehicle.

For the continuous version of HDSM-Ax change from baseline to end of therapy, assume the true mean difference between each BBI-4000 arm and the vehicle arm to be 0.18, with a common standard deviation of 0.36, i.e. an effect size (mean difference/standard deviation) of 0.50. With 100 evaluable subjects at a 1:1 ratio for each pairwise comparison between a BBI-4000 arm and the vehicle arm, the power is approximately 0.89 for observing a difference in favor of BBI-4000 at a 1-sided $p<0.10$ level. Same as for the binary version of HDSM-Ax, the gate keeping hierarchical testing algorithm will be employed for the continuous data.

Assuming an approximate 10% non-evaluable rate for the ITT primary efficacy analyses, 220 randomized subjects are targeted for enrollment.

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 5-digit subject number, this number will be composed of a 2-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 01001 as their assigned subject number; the subsequent subject from this site will have 01002 as their assigned subject number. The first subject from site 02 will have 02001 as their assigned subject number; the subsequent subject from this site will have 02002 as their assigned subject number. This number

will be unique to each subject and will be used to identify the subject throughout the study. This number is different from the randomization/kit number.

When subjects qualify for the study (determined by the investigator at the Rescreening Visit), they will be randomized to investigational product groups and will receive a randomization number. The kit carton and treatment plastic pumps have the randomization numbers displayed in their label.

The next eligible subject will be assigned the lowest available randomization number from the treatment kits available at the depot. In this manner, eligible subjects will be randomized to the investigational product sequence in accordance with the randomization schedule. The investigator will document the randomization/kit numbers in the source and on the CRF. The tear-off portion of the carton label from the outer carton (with blind-break panel) will be removed along the label perforation and placed into the study subject source file. In the event a subject is randomized at the Rescreening Visit but is not dispensed study medication (e.g. deemed ineligible at Baseline, withdraws consent, etc.) 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.

Subjects will be randomized to receive BBI-4000 5%, or 10%, or, 15% gel, or vehicle (placebo) gel in a balanced ratio of 1:1:1:1.

11.2 Compliance with Protocol

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

- Subjects will be asked if they have used the investigational product as instructed.
- Subjects will be asked if they experienced any problems dispensing the investigational product.
- Subjects will be asked if they used any products on their axillae (including antiperspirant/deodorant).
- Site staff will review concomitant medication use since the previous visit and determine if any concomitant medication use qualifies as a protocol deviation
- At Day 22 (Visit 8) and the End of Treatment Visit site staff will collect the dispensing container from the subject and record the weight of the 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 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 up to 56 days before 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 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 will be provided to Brickell Biotech.

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 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, 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 at least 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 at least 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 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. The product will be identified as an investigational compound, for external use. The study number and randomization 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 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 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, blinding, size, and endpoints of the study.

Authorized representatives of Brickell Biotech 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 as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the investigator and Brickell Biotech 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.

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: GRAVIMETRICALLY MEASURED SWEAT PRODUCTION

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

Set Up

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

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

Filter Paper Measurement

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

APPENDIX 2: HYPERHIDROSIS DISEASE SEVERITY SCALE (HDSS)

How would you rate the severity of your axillary hyperhidrosis?

☐	My sweating is never noticeable and never interferes with my daily activities	Score 1
☐	My sweating is tolerable but sometimes interferes with my daily activities	Score 2
☐	My sweating is barely tolerable and frequently interferes with my daily activities	Score 3
☐	My sweating is intolerable and always interferes with my daily activities	Score 4

APPENDIX 3: HYPERHIDROSIS DISEASE SEVERITY MEASURE-AXILLA (HDSM-AX)

Hyperhidrosis Disease Severity Measure--Axillary

(HDSM-Ax)

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

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

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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 because of your 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 because of your 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:

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., moist)

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. How normal was your level of physical exercise and stress since you woke up yesterday? (Please select all that apply.)

☐ It was a normal day in terms of physical exercise or stress.

☐ I experienced more physical exercise than usual.

☐ I experienced more nervousness, stress, or anxiety than usual.

☐ I experienced less physical exercise than usual.

☐ I experienced less nervousness, stress, or anxiety than usual.

APPENDIX 4: QUALITY OF LIFE ASSESSMENT

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.

DERMATOLOGY LIFE QUALITY INDEX-Axilla

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	❒

DERMATOLOGY LIFE QUALITY INDEX-Axilla

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

DERMATOLOGY LIFE QUALITY INDEX-Axilla

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

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

APPENDIX 5: TOLERABILITY ASSESSMENTS

These assessments are to be performed for both axillae 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 on 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 the 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 6: STUDY DRUG APPLICATION & SUBJECT INSTRUCTIONS

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

1. Expose the underarm areas and ensure they are dry. Don't wash the underarm areas prior to drying.
2. Carefully, by slowly applying pressure to the actuator with an index finger, place the gel of ONE full actuation to the dome of the white plastic applicator (provided).
3. Take the applicator introducing the three (3) middle fingers of the left hand in the plastic applicator hole and immediately apply study product to the right underarm area.
4. Distribute the product 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.
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 shower, shave or wash the underarm area at night then it should be at least 30 mins before study product application. Ensure the underarm areas are dry.
- 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, flame or smoking during the application and until the gel has dried. The subject should not expose the container to fire, flame or extreme heat.

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

- Do Not apply any product to your axilla (including deodorant).
- Exercise is to be avoided (e.g., gym, jogging, etc.).
- Avoid caffeine and tea until the gravimetric assessments is completed

SUBJECT INSTRUCTIONS

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

Contact:_____ At:_____

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

- Follow the instructions you are given and come to the study center for all visits with the study doctor or study staff.
- Tell the study doctor or study staff about any changes in your health or the way you feel.
- Tell the study doctor or study staff if you want to stop being in the study at any time.
- 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.
- Use only the non-antiperspirant deodorant provided to you.
- 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, flame or smoking during the application and until the gel has dried.
- **Do Not** expose the container to fire, flame or extreme heat.

Bring your Study Drug container to the clinic for study Visit 8 (Day 22) and to the End of Treatment Visit on Day 43 (Visit 13)

APPENDIX 7: EXAMPLE POTENT INHIBITORS OF CYP3A AND CYP2D6

Example Potent Inhibitors of CYP3A[a]		
apigenin	hydroxyzine	protease inhibitors
antipsychotics	interferon	ritonavir
candesartan	isoniazid	St. John's Wort[c] (and other herbal supplements)[b]
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[a]		
bupropion	fluoxetine	paroxetine
quinidine	terbinafine	

a) 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]
b) Prohibited medications (see section 6.2)
c) Discontinue within 30 days of the baseline visit for hyperhidrosis.