A Multi-Center, Open-Label Extension Study to Assess the Long-Term Safety, Tolerability and Pharmacokinetics of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to ≤17 Years of Age, Previously Enrolled in Study BBI-4000-CL-105

Compound:	Sofpironium Bromide Gel, 15%
US IND Number:	121256
Clinical Protocol Number:	BBI-4000-CL-108
Phase of Development:	2
Sponsor:	Brickell Biotech Inc. 5777 Central Ave., Suite 102 Boulder, CO 80301
Medical Monitor:	Brandon Kirsch, MD Brickell Biotech, Inc. 5777 Central Ave., Suite 102 Boulder, CO 80301 Phone: 720-619-4966
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Protocol Version:	Original 21 September 2018
Previous Protocol Versions:	Version / Version Date ( ) / ( ) ( ) / ( )

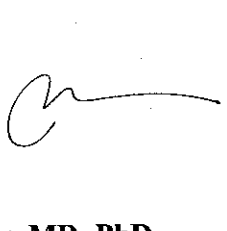
GCP Statement

This study will be conducted in accordance with the Food and Drug Administration (FDA) and International Council on Harmonisation (ICH) guidelines on current Good Clinical Practice (GCP), Good Laboratory Practice (GLP) guidelines, and the principles of the Declaration of Helsinki.

NCT03785587

SPONSOR SIGNATURE PAGE

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the clinical trial and complies with applicable regulations and Good Clinical Practice (GCP) standards.



Digitally signed by Patricia S. Walker MD, PhD-CSO
DN: cn=Patricia S. Walker MD, PhD-CSO, o=Brickell Biotech, Inc., ou=Management, email=pwalker@brickellbio.com, c=US
Date: 2018.09.21 23:43:09 +02'00'

Patricia Walker, MD, PhD
President and Chief Scientific Officer, Brickell Biotech

Date

AGREEMENT OF INVESTIGATOR COMPLIANCE

I have read the protocol entitled "A Multi-Center, Open-Label Extension Study to Assess the Long-Term Safety, Tolerability and Pharmacokinetics of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to ≤17 Years of Age, Previously Enrolled in Study BBI-4000-CL-105" and:

- Agree that the protocol contains all the information necessary to conduct the study;
- Agree to conduct the study in accordance with the protocol and as subsequently amended by the Sponsor (or designee), except when to protect the safety, rights or welfare of study subjects;
- Agree to conduct the study in accordance with applicable federal, state and local laws and regulations, and in accordance with the Food and Drug Administration (FDA) and International Council on Harmonisation (ICH) guidelines on current Good Clinical Practice (GCP), and the principles of the Declaration of Helsinki; and
- Agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator: Print Name	**Site ID Number**
Signature	**Date**

ABBREVIATIONS

Abbreviations	Definitions
AE	Adverse event
BP	Blood pressure
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
C_{max}	Maximum concentration
CRO	Contract Research Organization
C_{trough}	Trough concentration
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration
g	Grams
GCP	Good Clinical Practice
HDSM-Ax	Hyperhidrosis Disease Severity Measure-Axillary
HDSM-Ax, Child	Hyperhidrosis Disease Severity Measure-Axillary, Child
HIPAA	Health Insurance Portability and Accountability Act
hr, h, hrs	Hour(s)
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device

Abbreviations	Definitions
kg	Kilogram(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mm	Millimeter(s)
mmHg	Millimeter of mercury
NF	National Formulary
ng	Nanogram
nM	Nanomolar
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SRC	Study Review Committee
SSRI	Selective serotonin re-uptake inhibitors
TBV	Total blood volume
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
UPT	Urine pregnancy testing
US	United States of America
USP	United States Pharmacopeia
WHODD	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

Study Title	A Multi-Center, Open-Label Extension Study to Assess the Long-Term Safety, Tolerability and Pharmacokinetics of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, ≥9 to ≤17 Years of Age, Previously Enrolled in Study BBI-4000-CL-105
Study Number	BBI-4000-CL-108
Study Objectives	Primary Objectives: *Safety* To assess the long-term safety and tolerability of sofpironium bromide gel, 15% applied topically once daily for up to 24 weeks in children and adolescent subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis. *Pharmacokinetic* To assess the systemic exposure (C_{trough}) of sofpironium and its primary metabolite (BBI-4010), following topical application of ~0.67 mL of sofpironium bromide gel, 15% applied topically to each axilla, once daily (QD) for up to 24 weeks. Exploratory Objectives: • To assess the effect of topically applied sofpironium bromide gel, 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) and Hyperhidrosis Disease Severity Measure-Axillary, Child (HDSM-Ax, Child) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis • To assess the effect of topically applied sofpironium bromide gel, 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) Summary Questions; duration (No. 4) and severity (No. 5) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis • To assess the effect of topically applied sofpironium bromide gel, 15% on Patient Global Impression of Severity (PGI-S) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis • To assess the effect of topically applied sofpironium bromide gel, 15% on Patient Global Impression of Change (PGI-C) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis
Study Endpoints	Primary Endpoints: *Safety* • Incidence and severity of application site burning, itching, stinging, scaling and erythema • Incidence and severity of all adverse events (AEs) and their relationship to study drug • Incidence of clinically meaningful change from baseline in safety laboratory parameters, physical examinations, 12-lead electrocardiograms (ECGs) and vital signs • Proportion of subjects who discontinue treatment due to an AE *Pharmacokinetics*

	Determination of plasma concentrations (C_{trough}) of sofpironium, and BBI-4010, at Week 4 and Week 24 (end of treatment) following 24 weeks of QD topical application of sofpironium bromide gel, 15%. Exploratory Endpoints • Change of HDSM-Ax (≥12 years of age) or HDSM-Ax, Child (≥9 to <12 years of age) from baseline to end of treatment. • Change of HDSM-Ax Summary Questions; duration (No. 4) and severity (No. 5) from baseline to end of treatment. • Change of PGI-S from baseline to end of treatment. • PGI-C at Week 12 (Day 84) and end of treatment.
Study Assessments	Safety • Adverse events at all visits • Local application site tolerability assessments (including burning, itching, stinging, scaling and erythema) at all visits through and including Week 24 [Day 168], and Week 26 (Day 182), if applicable • Vital signs (heart rate [HR], blood pressure (BP), respiratory rate and temperature) at all visits through and including Week 26 • 12-lead ECG at Week 0 (Day 1), Week 4 (Day 28), Week 24 (Day 168), and Week 26 (Day 182), if applicable • Laboratory testing (hematology, chemistry and urinalysis) at Week 0 (Day 1), Week 4 (Day 28), Week 24 (Day 168), and Week 26 (Day 182), if applicable • Pregnancy test (females) at all visits through and including Week 26 (Day 182) • Abbreviated physical examination at all visits through and including Week 26 (Day 182) Pharmacokinetics • Plasma samples will be collected ≥12 hours after last dose on Week 0 (Day 1) [per Day 8/Visit 4 of Study BBI-4000-CL-105], Week 4 (Day 28), and Week 24 (Day 168). Efficacy • HDSM-Ax or HDSM-Ax, Child as assessed by the subject at all visits through and including Week 24 (Day 168) • HDSM-Ax or HDSM-Ax, Child Summary Questions; duration (No. 4) and severity (No. 5) as assessed by the subject at all visits through and including Week 24 (Day 168) • Change in PGI-S as measured by the subject at all visits through and including Week 24 (Day 168) • PGI-C as measured by the subject at Week 12 (Day 112) and Week 24 (Day 168)
Study Population	Subjects enrolled in this study will be males and females, ≥9 years to ≤17 years of age, with axillary hyperhidrosis who participated in and completed Study BBI-4000-CL-105.
Study Methodology	This multi-center, open-label extension study will evaluate the long-term safety, tolerability and pharmacokinetics of topical sofpironium bromide gel, 15%, when

	applied QD for up to 6 months in pediatric subjects ≥9 years to ≤17 years of age with axillary hyperhidrosis previously enrolled in Study BBI-4000-CL-105. Following completion of the initial PK and safety study (Study BBI-4000-CL-105), subjects will be provided the opportunity to enter this 6-month open-label extension study. Subjects will be screened for eligibility at Day 8 of Study BBI-4000-CL-105 (last PK sample collection under BBI-4000-CL-105 study). Therefore, for participating subjects, the final treatment visit (i.e., Day 8/Visit 4) of Study BBI-4000-CL-105 and the Screening/Enrollment visit (i.e., Week 0 [Day 1]) of Study BBI-4000-CL-108 (long-term extension study) will take place simultaneously. Subjects (parent/guardian) will be dispensed one container of sofpironium bromide gel, 15% each month at Visits 1-6. Subjects (and parent/guardian) will be instructed on the correct application procedure for sofpironium bromide gel, 15% (to be applied QD before bedtime to both axilla for up to 24 weeks). Vital signs, review of concomitant medications, assessment of AEs, completion of patient-reported outcomes (HDSM-Ax or HDSM-Ax, Child, and PGI-S), and urine pregnancy tests (UPT) for all females will be done each visit. Application site tolerability will be assessed at all visits through the end of treatment (EOT) at Week 24 (Day 168). Blood and urine for safety testing will be collected and analyzed at Week 4 (Day 28) and Week 24 (Day 168) for routine hematology, chemistry, and urinalysis parameters. ECGs will be assessed at Week 0 (pre-dose, Day 1), Week 4 (Day 28), and Week 24 (Day 168). A PK sample will also be collected at Week 4 (Day 28) and at Week 24 (Day 168). At Week 12 (Day 84) and at the end of treatment Week 26 (Day 168), the subject will also complete the PGI-C. A final visit will be conducted 2 weeks after the last application of study drug. Clinically significant abnormal laboratory parameters, and abnormal ECG noted at the previous visit, should be repeated at this visit. Comfort measures (e.g., topical analgesics and mechanical interference devices) may be used during all study blood collection events to reduce subject discomfort. A total of 8 scheduled visits will take place over approximately 26 weeks: Week 0 (Day 1), Week 4 (Day 28), Week 8 (Day 56), Week 12 (Day 84), Week 16 (Day 112), Week 20 (Day 140), Week 24 (Day 168), and Week 26 (Day 182). Subjects who prematurely discontinue study drug will complete the EOT (Week 24/Visit 7) visit. An internal Study Review Committee (SRC), comprising the Sponsor Medical Monitor, Lead Investigator and Contract Research Organization (CRO) Medical Monitor, will facilitate the management and identification of potential safety concerns, will assess whether revisions to the study protocol and/or consent are required, and will evaluate the overall progress of the study.
Description of Test Article, Dosage, and Administration	All subjects will receive active study drug. One dose of sofpironium bromide gel, 15% will be applied topically using the supplied applicator to each axilla QD at approximately the same time before bedtime for up to 24 weeks. Sofpironium bromide gel is packaged in airless, multi-dose, metered pump containers. Each administration of sofpironium bromide gel, 15% is ~0.67 mL and contains 86.5 mg of sofpironium bromide, for a total daily dose when applied to both axillae of 173 mg.
Duration of Study Participation	Each subject will participate in the study for up to 26 weeks: • Screening (Day 1)[1] • Treatment (24 weeks) • Follow-up (2 weeks after last dose) [1] Subjects enrolled in Study BBI-4000-CL-105 opting to enroll in this extension study will continue receiving study drug in the extension study. The screening visit of Study

	BBI-4000-CL-108 (Week 0/Day 1) and end of treatment (EOT) visit of Study BBI-4000-CL-105 (Visit 4/Day 8) will be conducted simultaneously.
Study Centers	Up to 10 investigational sites in the United States (US) who participate in Study BBI-4000-CL-105 will be eligible to participate in this study.
Main Inclusion Criteria	For a study subject to be evaluated for study participation: 1. Written Informed Consent (including HIPAA) will be obtained from the Parent(s)/Legal Guardian(s) prior to the conduct of any study related procedures to permit participation of a minor in a clinical research study in accordance with federal and local laws. Additionally, assent from a minor child will be obtained in accordance with federal and local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Study subjects will be eligible for inclusion in the study if they meet all the following criteria at Screening/Enrollment (Week 0 [Day 1]) as applicable: 2. Are male or female ≥9 to ≤17 years of age at the time of consent. 3. Have enrolled and completed treatment in Study BBI-4000-CL-105 and met all inclusion/exclusion criteria, were compliant with study procedures (e.g., visits and PK sample collection), and did not experience any clinically significant AEs that would preclude safe continuation of study drug for up to an additional 24 weeks. 4. Continue to be in generally good health based on Investigator's assessment (other than axillary hyperhidrosis), with no clinically significant laboratory abnormalities, co-morbidities or psychiatric conditions which, in the opinion of the Investigator, would place the subject at increased risk or would confound the objectives of the study. 5. The Parent(s)/Legal guardian(s) and study subject are willing and able to follow all study-related procedures, including but not limited to application of study drug and venipuncture and are willing and able to return to the study clinic for required study visits. 6. If female, must be willing to take monthly pregnancy tests during the study. 7. Sexually active females must agree to use a medically acceptable method of contraception while receiving study drug. For purposes of this study, all female subjects are considered of childbearing potential as axillary hyperhidrosis generally occurs in post-pubescent individuals. Acceptable contraceptive methods include the following: a. Abstinence for the duration of the study or where partner is sterile (e.g., vasectomy) is an acceptable form of contraception. b. Hormonal contraception, including oral, injectable, or implantable methods started at least 2 months prior to screening, or c. Two forms of non-hormonal contraception, including intrauterine devices (IUD) (at least 1-week status post placement) and properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents, etc.). The Investigator will educate the subject regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

Main Exclusion Criteria	A study subject will be excluded from the study if they meet any of the following criteria at Screening/Enrollment (Week 0 [Day 1]): 1. In the Investigator's opinion, any clinically significant systemic or local skin reaction related to use of the study drug. 2. Subcutaneous tissue conditions of the axilla(e), (i.e., the axillary area should be deemed otherwise "normal", besides the hyperhidrosis diagnosis, and free of blisters, large boils or sinus tracts, significant scarring or open wounds). 3. Has received any prohibited medication(s) or procedure(s) under Study BBI-4000-CL-105 prior to Screening/Enrollment. 4. Subject is pregnant, lactating or is planning to become pregnant during the study. 5. Positive drug or alcohol screen while enrolled in Study BBI-4000-CL-105.

Statistical Analysis	Sample Size Sample size is based on the planned enrollment under Study BBI-4000-CL-105. Up to 24 subjects may participate in this study. Analysis Populations Two populations will be used for analysis: Safety and PK. The definition of these populations follows: • **Safety Population**: All enrolled subjects who applied at least one dose of study drug and have at least one post-baseline safety assessment • **Pharmacokinetic Population**: All enrolled subjects who applied at least one dose of study drug and have at least one quantifiable PK sample for analysis Primary Analysis *Safety* The Safety Population will be used for evaluation of safety assessments, which consists of reported AEs, application site local tolerability assessments, vital signs, physical examinations, 12-lead ECG, and laboratory measurements (hematology, chemistry, and urinalysis). Full details will be specified in the statistical analysis plan (SAP). *Pharmacokinetics* Individual plasma concentrations of sofpironium and BBI-4010 will be listed and summarized descriptively including arithmetic mean, standard deviation (SD), Coefficient of Variation (CV, %), median, minimum and maximum values. Full details of the analysis will be specified in the SAP. Exploratory *Efficacy* • The HDSM-Ax or HDSM-Ax, Child total score will be descriptively summarized for values at each visit and for changes from baseline. Baseline will be considered the Day 1 pre-dose evaluation under Study BBI-4000-CL-105. • The HDSM-Ax or HDSM-Ax, Child Summary Questions; duration (No. 4) and severity (No. 5) will be descriptively summarized for values at each visit and for changes from baseline. Baseline will be considered the Day 1 pre-dose evaluation under Study BBI-4000-CL-105. • The PGI-S will be descriptively summarized for values at each visit and for changes from baseline. Baseline will be considered the Day 1 pre-dose evaluation, under Study BBI-4000-CL-105. • The PGI-C at Week 12 (Day 84) and Week 24 (Day 168), end of treatment will be summarized. Full details will be specified in the SAP.

SCHEDULE OF ACTIVITIES

Description	Screening/ Enrollment	Treatment					End of Treatment/Early Termination	End of Study
Week	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**
Study Day (±days)/ Visit	**Day 1/ Visit 1**	**Day 28 (±3)/ Visit 2**	**Day 56 (±5)/ Visit 3**	**Day 84 (±5)/ Visit 4**	**Day 112 (±5)/ Visit 5**	**Day 140 (±5)/ Visit 6**	**Day 168 (±5)/ Visit 7**	**Day 182 (±5)/ Visit 8**
Consent/Assent Refer to Section 6.1	X							
Inclusion/Exclusion criteria Refer to Sections 5.1 and 5.2	X							
Demographics Refer to Section 6.2	X [a]							
Height/Weight Refer to Section 6.5	X [a]							
Abbreviated Physical Examination Refer to Section 6.4	X [b]	X					X	X
Medical/Medication History Refer to Section 6.3	X [b]							
Vital Signs Refer to Section 6.7	X [b]	X	X	X	X	X	X	X
HDSM-Ax and HDSM-Ax, Child Refer to Section 6.8	X [a]	X	X	X	X	X	X	X
PGI-S Refer to Section 6.10	X [a,b]	X	X	X	X	X	X	X
PGI-C Refer to Section 6.11				X			X	
Safety laboratory testing Refer to Section 6.12.4.2	X [a,b]	X					X	X [d]
Pregnancy testing (females only) Refer to Section 6.12.4.1	X [b]	X	X	X	X	X	X	

Description	Screening/ Enrollment	Treatment					End of Treatment/Early Termination	End of Study
Week	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**
Study Day (±days)/ Visit	**Day 1/ Visit 1**	**Day 28 (±3)/ Visit 2**	**Day 56 (±5)/ Visit 3**	**Day 84 (±5)/ Visit 4**	**Day 112 (±5)/ Visit 5**	**Day 140 (±5)/ Visit 6**	**Day 168 (±5)/ Visit 7**	**Day 182 (±5)/ Visit 8**
Pharmacokinetic sampling Refer to Section 6.12.5	X [b]	X [c]					X [c]	
12-lead ECG Refer to Section 6.8	X [b]	X					X	X [d]
Concomitant Medications Refer to Section 6.13	X [b]	X	X	X	X	X	X	X
AE Assessment Refer to Section 10	X [b]	X	X	X	X	X	X	X
Application Site Tolerability Assessment Refer to Section 6.6	X [b]	X	X	X	X	X	X	
Dosing Refer to Sections 8.4 and 8.5 and Study drug application and dosing diary card completion Refer to Appendix C	←	—	—	—	—	—	→	
Compliance Refer to Section 8.5	X [b]	X	X	X	X	X	X	
Study Drug Dispensing Refer to Section 8.3	X	X	X	X	X	X		

[a] Baseline data (prior to first dose) collected under BBI-4000-CL-105 will be carried over to the current study.
[b] Data collected at End of Treatment (Day 8 [±1 day]) under BBI-4000-CL-105 will be carried over to the current study.
[c] Collection ≥12 hours from evening application of drug.
[d] Only collect if abnormal at Visit 7/Early Termination Visit.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Background

Sofpironium bromide (BBI-4000) is a novel soft-anticholinergic ester analog of glycopyrrolate in development for the topical treatment of primary axillary hyperhidrosis.

1.2 Rationale

The pediatric pharmacokinetic and safety study (BBI-4000-CL-105) that precedes this long-term safety extension study, is a short treatment duration (7 days [±1 day]) PK study. The purpose of this study is to collect additional safety and tolerability information on children and adolescents following once daily sofpironium bromide gel, 15% treatment for up to 24 wks. Furthermore, subjects enrolled in Study BBI-4000-CL-105 may only begin to perceive improvement of symptoms near its conclusion. Therefore, subjects who complete Study BBI-4000-CL-105 will be allowed the opportunity to participate in this long-term extension study (i.e., 24 weeks of treatment) in which they may potentially experience additional clinical benefit from sofpironium bromide gel, 15%. The data collected will further inform enhance the pediatric safety and tolerability profile of the study drug.

1.3 Risk / Benefit Assessment

The results to date of the clinical program support the safe use of sofpironium bromide gel, 15% for the treatment of primary axillary hyperhidrosis. Ten clinical studies have been conducted with sofpironium bromide gel exposing over 700 adult subjects to the active ingredient: two Phase 1 studies in healthy adults, four Phase 1 and three Phase 2 studies in adults with primary axillary hyperhidrosis, and a Phase 2 study in adults with primary palmar hyperhidrosis.

Sofpironium bromide has consistently demonstrated low incidence of treatment-emergent adverse events (TEAEs) following daily application for periods of time up to 6 weeks. Most AEs have been mild and transient, with all resolving after treatment discontinuation. A long-term safety study (BBI-4000-CL-303) to evaluate the safety and tolerability of sofpironium bromide gel, 15% in subjects ≥12 years of age has been initiated and is ongoing at this time.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

3.1.1.1 Safety

To assess the long-term safety and tolerability of sofpironium bromide gel, 15% applied topically once daily for up to 24 weeks in children and adolescent subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis.

3.1.1.2 Pharmacokinetics

To assess the systemic exposure (C_{trough}) of sofpironium and its primary metabolite (BBI-4010) following topical application of ~0.67 mL of sofpironium bromide gel, 15% applied topically to each axilla, once daily (QD) for up to 24 weeks.

3.1.2 Exploratory Objectives

- To assess the effect of topically applied sofpironium bromide gel, 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) and Hyperhidrosis Disease Severity Measure-Axillary, Child (HDSM-Ax, Child) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis
- To assess the effect of topically applied sofpironium bromide gel, 15% on Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) Summary Questions; duration (No. 4) and severity (No. 5) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis
- To assess the effect of topically applied sofpironium bromide gel, 15% on Patient Global Impression of Severity (PGI-S) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis
- To assess the effect of topically applied sofpironium bromide gel, 15% on Patient Global Impression of Change (PGI-C) in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis

3.2 Criteria for Evaluation

3.2.1 Primary Endpoints

3.2.1.1 Safety

- Incidence and severity of application site burning, itching, stinging, scaling and erythema
- Incidence and severity of all AEs and their relationship to study drug
- Incidence of clinically meaningful change from baseline in safety laboratory parameters, 12-lead electrocardiograms (ECGs) and vital signs
- Proportion of subjects who discontinue treatment due to an AE

3.2.1.2 Pharmacokinetics

- Determination of plasma concentrations (C_{trough}) of sofpironium, and BBI-4010 at Week 4 and Week 24 (end of treatment) following 24 weeks of QD topical application of sofpironium bromide gel, 15%.

3.2.2 Exploratory Endpoints

- Change of HDSM-Ax (≥12 years of age) or HDSM-Ax, Child (≥9 to <12 years of age) from baseline to end of treatment
- Change of HDSM-Ax Summary Questions; duration (No. 4) and severity (No. 5) from baseline to end of treatment.
- Change of PGI-S from baseline to end of treatment
- PGI-C at Week 12 (Day 84) and end of treatment

4 STUDY DESIGN

4.1 General Description

This multi-center, open-label extension study will evaluate the long-term safety, tolerability, and pharmacokinetics of sofpironium bromide gel, 15%, when applied QD for up to 6 months in pediatric subjects ≥9 years to ≤17 years of age with axillary hyperhidrosis previously enrolled in Study BBI-4000-CL-105.

Following completion of the initial PK and safety study (Study BBI-4000-CL-105), subjects will be provided the opportunity to enter this 6-month open-label extension study. Subjects will be screened for eligibility at Day 8 of Study BBI-4000-CL-105 (last PK sample collection under BBI-4000-CL-105 study). Therefore, for participating subjects, the final treatment visit (i.e., Day 8/Visit 4) of Study BBI-4000-CL-105 and the Screening/Enrollment visit (i.e., Week 0 [Day 1]) of Study BBI-4000-CL-108 (long-term extension study) will take place simultaneously.

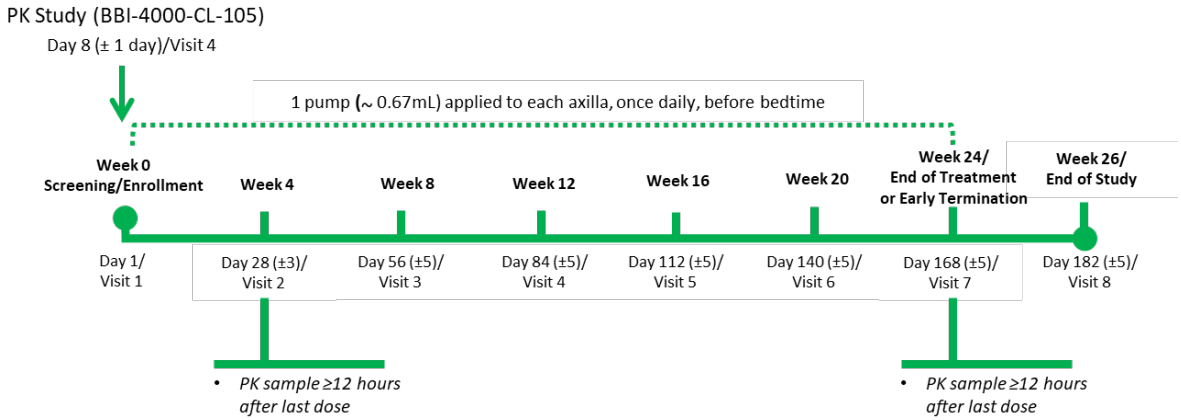
Subjects (parent/guardian) will be dispensed one container of sofpironium bromide gel, 15% each month at Visits 1-6. Subjects (and parent/guardian) will be instructed on the correct application procedure for sofpironium bromide gel, 15% (to be applied QD before bedtime to both axilla for up to 24 weeks).

Vital signs, review of concomitant medications, assessment of AEs, completion of patient-reported outcomes (HDSM-Ax or HDSM-Ax, Child, and PGI-S), and urine pregnancy tests (UPT) for all females will be done each visit. Application site tolerability will be assessed at all visits through the end of treatment (EOT) at Week 24 (Day 168 [±5 days]). Blood and urine for safety testing will be collected and analyzed at Week 4 (Day 28 [±3 days]) and Week 24 (Day 168 [±5 days]) for routine hematology, chemistry, and urinalysis parameters. ECGs will be assessed at Week 0 (pre-dose, Day 1), Week 4 (Day 28 [±3 days]), and Week 24 (Day 168[±5 days]). A PK sample will also be collected at Week 4 (Day 28 [±3 days]) and at Week 24 (Day 168 [±5 days]). At Week 12 (Day [84 ±5 days]) and at the end of treatment at Week 24 (Day [162 ±5 days]), the subject will also complete the PGI-C. A final visit will be conducted 2 weeks after the last application of study drug. Clinically significant abnormal laboratory parameters, and abnormal ECG noted at the previous visit, should be repeated at this visit. Comfort measures (e.g., topical analgesics and mechanical interference devices) may be used during all study blood collection events to reduce subject discomfort.

A total of 8 scheduled visits will take place over approximately 26 weeks: Week 0 (Day 1), Week 4 (Day 28 [±3 days]), Week 8 (Day 56 [±5 days]), Week 12 (Day 84 [±5 days]), Week 16 (Day 112 [±5 days]), Week 20 (Day 140 [±5 days]), Week 24 (Day 168 [±5 days]), and Week 26 (Day [182 ±5 days]). Subjects who prematurely discontinue study drug will complete the EOT (Week 24/Visit 7) visit.

An internal Study Review Committee (SRC), comprising the Sponsor Medical Monitor, Lead Investigator and Contract Research Organization (CRO) Medical Monitor, will facilitate the management and identification of potential safety concerns, will assess whether revisions to the study protocol and/or consent are required, and will evaluate the overall progress of the study.

Figure 1 Study Schematic



4.2 Screening and Enrollment

Subjects enrolled in this study will be males and females, ≥9 to ≤17 years of age, with axillary hyperhidrosis who participated and completed treatment in Study BBI-4000-CL-105. Up to 24 subjects may participate in this study.

4.3 Screen Failure

A subject who has been screened but subsequently fails to meet the inclusion/exclusion criteria prior to receipt of study drug in this study will be deemed a screen failure.

4.4 Completion

Each subject will participate in the study for up to approximately 26 weeks, from the time the informed consent form (ICF) is signed/assent provided (Visit 1) through the final visit (Week 26 [Day 182 (±5 days)]).

4.5 Early Termination (ET)

A subject or the subject's parent/guardian may withdraw the subject from treatment or from the study at any time upon request or the subject may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

4.5.1 Criteria for Premature Discontinuation

4.5.1.1 Discontinuation from Treatment

A subject must be permanently discontinued from the study drug for any of the following reasons:

- The subject becomes pregnant.
- Allergic or adverse reaction to the study drug.
- Clinically significant AE, which in the opinion of the Investigator, or SRC, would put the subject at unnecessary risk if dosing was continued.
- The subject's axillary hyperhidrosis worsens and requires alternative or supplemental medication during the study.

If a subject is discontinued from treatment, he or she should continue to be followed in the study per the SCHEDULE OF ACTIVITIES. If subject refuses to stay in the study, then he or she will be encouraged to complete the Early Termination Visit 7 study procedures.

4.5.1.2 Discontinuation from Study

A subject must be discontinued from study drug and from the study for the following reason:

- The subject withdraws consent. From the time consent is withdrawn, no additional data should be collected. However, the Sponsor may retain and continue to use data collected before such withdrawal of consent.

A subject may be discontinued from the study drug or from the study for the following reason:

- The subject requests withdrawal from the study. For the safety of the subject, if withdrawal is requested, the subject should be encouraged to complete the Early complete the Early Termination Visit 7 study procedures.

4.5.1.3 Lost to Follow-up

A subject is considered to have been lost to follow-up if he/she [subject or parent/legal guardian] cannot be contacted by the Investigator (or designee) after 3 documented attempts. The Investigator (or designee) will document efforts to attempt to reach the subject/ parent/guardian. The end of participation for a subject lost to follow-up is documented as the date of the last visit.

4.5.1.4 Subject Replacement

Subjects who prematurely discontinue will not be replaced.

4.6 Safety Oversight

4.6.1 Study Review Committee (SRC)

An internal SRC, comprising the Sponsor Medical Monitor, Lead Investigator and CRO Medical Monitor, will facilitate the management and identification of potential safety concerns and will assess whether revisions to the study protocol and/or consent are required and will evaluate the overall progress of the study.

4.6.2 Investigator

The Investigator must have access and be available to promptly review the results of all safety assessments (i.e., clinical laboratory testing), ECG results, vital signs and AEs including application site assessment information throughout the study. Safety assessments must be promptly entered into the Electronic Data Capture (EDC) system (if possible, within 48 hours of notification of event). Clinical laboratory data will be evaluated by the Investigator and clinical relevance will be assessed for abnormal values and the assessment will be documented on the laboratory report. A copy of the reports will be maintained as part of the source documentation.

5 STUDY SUBJECT SELECTION

5.1 Inclusion Criteria

For a study subject to be evaluated for study participation:

1. Written Informed Consent (including HIPAA) will be obtained from the Parent(s)/Legal Guardian(s) prior to the conduct of any study related procedures to permit participation of a minor in a clinical research study in accordance with federal and local laws. Additionally, assent from a minor child will be obtained in accordance with federal and local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB)/Institutional Ethics Committee (EC).

Study subjects will be eligible for inclusion in the study if they meet all the following criteria at Screening/Enrollment (Week 0 [Day 1]) as applicable:

2. Are male or female ≥9 to ≤17 years of age at the time of consent.
3. Have enrolled and completed treatment in Study BBI-4000-CL-105 and met all inclusion/exclusion criteria, were compliant with study procedures (e.g., visits and PK sample collection) and did not experience any clinically significant AEs that would preclude safe continuation of study drug for up to an additional 24 weeks.
4. Continue to be in generally good health based on Investigator's assessment (other than axillary hyperhidrosis), with no clinically significant laboratory abnormalities, co-morbidities or psychiatric conditions which, in the opinion of the Investigator, would place the subject at increased risk or would confound the objectives of the study.
5. The Parent(s)/Legal guardian(s) and study subject are willing and able to follow all study-related procedures, including but not limited to application of study drug and venipuncture and are willing and able to return to the study clinic for required study visits.
6. If female, must be willing to take monthly pregnancy tests during the study.
7. Sexually active females must agree to use a medically acceptable method of contraception while receiving study drug. For purposes of this study, all female subjects are considered of childbearing potential as axillary hyperhidrosis generally occurs in post-pubescent individuals. Acceptable contraceptive methods include the following:
    a. Abstinence for the duration of the study or where partner is sterile (e.g., vasectomy) is an acceptable form of contraception.
    b. Hormonal contraception, including oral, injectable, or implantable methods started at least 2 months prior to screening, or
    c. Two forms of non-hormonal contraception, including intrauterine devices (IUD) (at least 1-week status post placement) and properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents, etc.).

The Investigator will educate the subject regarding abstinence or contraception options and the correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

5.2 Exclusion Criteria

A study subject will be excluded from the study if they meet any of the following criteria at Screening/Enrollment (Week 0 [Day 1]).

1. In the Investigator's opinion, any clinically significant systemic or local skin reaction related to use of the study drug.
2. Subcutaneous tissue conditions of the axilla(e), (i.e., the axillary area should be deemed otherwise "normal", besides the hyperhidrosis diagnosis, and free of blisters, large boils or sinus tracts, significant scarring or open wounds).
3. Has received any prohibited medication(s) or procedure(s) under Study BBI-4000-CL-105 prior to Screening/Enrollment.
4. Subject is pregnant, lactating or is planning to become pregnant during the study.
5. Positive drug or alcohol screen while enrolled in Study BBI-4000-CL-105.

6 DESCRIPTION OF STUDY PROCEDURES

A description of study procedures and frequency are listed in the SCHEDULE OF ACTIVITIES and is provided within the content of this protocol.

6.1 Obtaining Informed Consent

6.1.1 Written Parental/Legal Guardian Consent

Adequate provisions must be made for soliciting the permission of the subject's parent(s) or legally authorized representative/guardian. If a subject turns 18 years of age during the course of the study, written informed consent will be obtained from the subject at the next visit.

The process for obtaining oral and/or written assent for children and adolescents is similar to that of obtaining consent for adults. An effective informed consent process involves at minimum these elements:

- Conducting the process in a manner and location that ensures privacy;
- Giving adequate information about the study in a language understandable to the parent/legal guardian and child/adolescent;
- Providing adequate opportunity for the parent/legal guardian and child/adolescent to consider all options;
- Responding to the parent(s)/legal guardian(s) and child's/adolescent's questions;
- Ensuring the parent/legal guardian and child/adolescent has understood the information provided;
- Obtaining the parent/legal guardian and child/adolescent voluntary agreement to participate, and
- Continuing to provide information to parent(s)/legal guardian(s), child/adolescent as new information regarding this research program becomes available that may affect their willingness to continue in this study.

6.1.2 Minimum Federal Requirements for Consent

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will determine the permissions (one or both parents/legal guardian(s)) required for participation of a minor in this study based on level of risk (e.g., minimal or greater than minimal).

6.1.3 When Parents/Legal Guardians Disagree

If there are two parents/legal guardians available to give permission but they disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. This applies even if only one parent's (guardian's) signature is required. When both parents (guardians) are involved in the decision, they must agree for the child to be enrolled. If a parent who was not involved or available for the original consent later becomes involved or available, the two parents (guardians) must then agree.

6.1.4 Assent

The Investigator should carefully consider and propose adequate provisions for obtaining assent of children and adolescents prior to their participating in research. In general, assent is usually obtained from a child ≥ 7 years of age, however the approving IRB/IEC will determine whether or how assent will be obtained. The child should be provided with essential information and asked if they wish to participate in the research study.

6.1.5 Documenting the Consent/Assent Process

Consent/Assent MUST be obtained and documented PRIOR to initiation of any study procedures. The Principal Investigator or his/her approved designee must explain the nature of the study and associated risks to the parent(s)/legal guardian and study subject. The date/time that the informed consent is signed, a brief description of the consent/assent process (e.g., questions asked by the subject), and the name of the individual who obtained consent will be recorded in the source record. A copy of the signed informed consent should be provided to the parent(s)/legal guardian. Depending on the approving IRB and local requirements, an assent form may be included as part of the consent and may or may not be required to be signed by the child. Investigators must adhere to their local requirements for proper documentation of consent/assent. A summary of assent procedures for execution of this study must be maintained in the Investigator Essential Regulatory File. It is the responsibility of the Principal Investigator to ensure that any individual delegated the responsibility for obtaining consent/assent are familiar and adhere to the applicable consent/assent requirements.

6.2 Demographics

Subject demographic information will be recorded at Screening/Enrollment (Week 0 [Day 1]). Demographic information will include date of birth, gender (at the time of birth), race, and ethnicity. Findings will be documented in the source documentation and the eCRF.

6.3 Histories

6.3.1 General Medical/Surgical and Social History

Relevant medical and surgical history will be recorded at Screening/Enrollment (Week 0 [Day 1]) and will include medical diagnoses, major surgical procedures within the last 3

years. Social history (i.e., tobacco, drug, and alcohol use) and allergies (i.e., food, medications and environmental) will also be recorded at screening. Findings will be documented in the source documentation and the eCRF.

6.3.2 History – Hyperhidrosis

The parent/guardian and subject will provide historical information pertaining to the diagnosis of axillary hyperhidrosis, including date of diagnosis.

6.3.3 Medication History

Medications taken within the last month (30 days) prior to first dose of sofpironium bromide gel, 15% under Study BBI-4000-CL-105 and within 1 week prior to Screening/Enrollment (Week 0 [Day 1]) will be recorded in the source document and on the eCRF. Also refer to Section 6.13 concomitant medications and restrictions for additional information.

6.4 Abbreviated Physical Examination

The abbreviated physical examination will include an examination of general appearance, skin (including specific evaluation of axillary vaults), lungs, and heart. Additional systems will be evaluated as needed. Physical exam findings must be recorded in the source documentation and include the date and name of the individual conducting the examination. Physical examinations must be performed by an individual licensed to conduct standard physical examinations. An examination will be done at every visit.

6.5 Height and Weight

Height and weight will be collected at Baseline, prior to first dose, collected under BBI-4000-CL-105, and will be carried over to the current study.

6.6 Application Site Tolerability Assessment

Application site tolerability assessments will be evaluated through assessment of symptoms at the drug-application site. These assessments are to be performed for each axilla individually. Subject assessments will be made prior to the Investigator assessments (Appendix F).

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

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

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

6.7 Vital Signs

Vital signs will be taken at every visit.

6.7.1 Temperature and Respiratory Rate

Temperature (oral or oral equivalent) and respiratory rate will be recorded once at each scheduled time point. Findings will be recorded in the source documentation and in the eCRF.

6.7.2 Seated Blood Pressure and Heart Rate

Blood pressure should always be measured on the SAME arm (location should be documented) and with an appropriately sized (e.g., pediatric cuff) blood pressure cuff (that should be the same sized cuff throughout the study) for accurate comparison of readings over time. Position is critical for accurate BP measurements. Therefore, when the BP is measured, the arm (cuff) should be at the level of the heart. When seated, feet should be flat on the floor (if possible) with back supported and arm supported at the level of the heart (e.g., resting on a table). Blood pressure (systolic/diastolic) and HR will be assessed after the study subject has rested in a seated position for at least five (5) minutes.

It is important that vital signs be taken either before a meal, or at least 30 minutes after a meal or consuming caffeine containing products.

6.8 Twelve-Lead Electrocardiogram (ECG)

Investigative sites will use a calibrated ECG machine to obtained ECGs. The ECG paper speed will be set to 25 mm/second. Site personnel must assess the quality of the ECG while the subject is still at the investigative site in the event that an additional ECG needs to be performed (i.e., if artefact is present). Subject QT intervals will be reported as corrected for HR according to the Fridericia Formula (QTcF).

TWO ORIGINAL IDENTICAL ECGs should be printed (1 source and 1 for Sponsor) and labelled with Subject ID, and collection timepoint. The Investigator will read, provide interpretation, and sign and date the source document ECG.

For younger children who have difficulty lying still, the parent/guardian (caregiver) should practice prior to the Day 1 study visit. It is suggested that parents/guardians be instructed on the use of a timer to help the child understand how long to hold still. If possible, have the subject rest quietly for at least 10 minutes.

ECGs will be done at Week 0 (Day 1) [data to carry over from Day 8/Visit 4 of Study BBI-4000-CL-105], Week 4 (Day 28 [±3 days]), Week 24 (Day 168 [±5 days]) and Week 26 (Day 182 [±5 days]), if abnormal at Week 24.

6.9 Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax)

The HDSM-Ax (Appendix B) was developed to determine the severity of excessive sweating in patients ≥12 years of age with primary axillary hyperhidrosis. The HDSM-Ax is a well-developed, validated measure of patient-reported signs and symptoms that quantifies changes in symptom severity in response to treatment (Kirsch, 2018). A child version (refer to Appendix A) suitable for use in children ≥9 to <12 years of age (HDMX-Ax, Child), will also be used in this study. The subject will be asked to complete the first 5 questions. Measure will be assessed at Week 0 (pre-dose Day 1), Week 4 (Day 28 [±3 days]), Week 8

(Day 46 [±5 days]), Week 12 (Day 84 [±5 days]), Week 16 (Day 112 [±5 days]) Week 20 (Day 140 [±5 days]), and Week 24 (Day 168 [±5 days]) and Week 26 (Day 182 [±5 days]).

6.10 Patient Global Impression of Severity (PGI-S)

All subjects will be asked to complete one question pertaining to the severity of underarm sweating over the past week (refer to Appendix A, No. 6 and Appendix B, No. 6). Measure will be assessed at Week 0 (pre-dose Day 1), Week 4 (Day 28 [±3 days]), Week 8 (Day 46 [±5 days]), Week 12 (Day 84 [±5 days]), Week 16 (Day 112 [±5 days]) Week 20 (Day 140 [±5 days]), Week 24 (Day 168 [±5 days]) and Week 26 (Day 182 [±5 days]).

6.11 Patient Global Impression of Change (PGI-C)

All subjects will be asked to complete one question pertaining to the overall change in underarm sweating since the subject started the study drug (refer to Appendix A, No. 7 and Appendix B, No. 7). Measure will be assessed at Week 12 (Day 84 [±5 days]) and the end of treatment, Week 24 (Day 168 [±5 days]).

6.12 Laboratory Testing

6.12.1 Testing Facilities

Blood samples for routine safety laboratory testing will be analyzed by a centralized laboratory that is certified under the Clinical Laboratory Improvement Act (CLIA).

6.12.2 Sample Collection and Blood Volumes

Blood samples will be collected via venipuncture. Measures should be taken to minimize discomfort during sample collection including but not limited to diversion or use of a topical anesthetic (supplied).

Total blood volume (TBV) is related to body weight. The TBV of a child is approximately 75-80 mL/kg. Existing guidelines for blood sample volume limits (ranging from 1–5% of total blood volume within 24 hours and up to 10% of total blood volume over 8 weeks) are consistent with the limited evidence available on “minimal risk” to children (Howie, 2011).

In this study, the smallest volume of blood possible will be collected for analysis of safety and PK. Blood samples are scheduled to be collected Week 4 (Day 28 [±3 days]) and Week 24 (Day 168 [±5 days]). Approximately 6 mL will be collected for safety, and approximately 2 mL for PK at each collection time point. Laboratory tests may be repeated as clinically indicated at Week 26 (Day 182 [±5 days]).

6.12.3 Sample Identification

Blood samples will be labeled with the subject ID, sample collection date/time, and sample type. The Sponsor will not have any information that would identify the study subject.

6.12.4 Screening and Safety Laboratory Testing

6.12.4.1 Pregnancy Testing

A pregnancy test is required for all female subjects. A UPT (local) will be done at all visits through Week 24 (Day 168 [±5 days]). Testing will be performed utilizing CLIA waived methodology. Testing supplies will be provided by the Sponsor to be used locally at the site.

6.12.4.2 Routine Safety Laboratory Testing

The following safety laboratory panel will be collected at Week 0 (Day 1) [data to carry over from Day 8/Visit 4 of Study BBI-4000-CL-105], Week 4 (Day 28 [±3 days]), and Week 24 (Day 168 [±5 days]). Laboratory tests may be repeated as clinically indicated at Week 26 (Day 182 [±5 days]) and analyzed by a central reference laboratory. Safety laboratory samples will be collected in accordance with the Schedule of Activities. Additional samples may be collected and analyzed as clinically indicated. Details regarding collection, shipping and reporting of results will be provided in the Laboratory Reference Manual.

Table 1 Safety Laboratory Panel

Hematology		
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)	Neutrophils
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin		Eosinophils
Hematocrit		Basophils
Clinical Chemistry		
Blood urea nitrogen (BUN)	Chloride	Alkaline phosphatase
Creatinine	Aspartate aminotransferase (AST)	Total and direct bilirubin
Sodium	Alanine aminotransferase (ALT)	
Potassium	Gamma-glutamyl transferase (GGT)	*Serum Pregnancy at Screen for females only
Routine Urinalysis		
Specific gravity		
pH, glucose, protein, blood and ketones by dipstick		
Microscopic examination (if blood or protein is abnormal)		
Pregnancy Testing		
Urine pregnancy testing for females only		

6.12.5 Pharmacokinetics

Approximately 2 mL of blood will be collected for PK analysis at Week 0 (Day 1) [per Day 8/Visit 4 of Study BBI-4000-CL-105], Week 4 (Day 28 [±3 days]) and Week 24 (Day 168 [±5 days]). Samples will be collected ≥12 hours from the time of dosing with study drug. Details regarding collection, processing, shipping and storage of PK samples will be provided in the laboratory reference manual.

6.13 Concomitant Medications

6.13.1 General

Use of chronic medications or as-needed medications (e.g., acetaminophen, topical anesthetic [EMLA]) will be permitted during the screening and active study period (unless otherwise

restricted, refer to Section 6.13.2), and should be recorded in the source document and on the eCRF. Any changes in concomitant medication usage will be recorded in the source documents and on the eCRF. If the reason for change is related to an AE, the event should be recorded in the source documents and as an AE in the eCRF.

6.13.2 Concomitant Medication Restrictions

The following medications will not be permitted during the study period:

- Botulinum toxin to the axillary area
- Newly prescribed anti-anxiety, anti-depressant, and/or psychostimulants (e.g., amphetamine) or drugs with known anticholinergic side effects
- Any cholinergic drug (e.g., bethanechol)
- Newly prescribed serotonergic agonist (or drugs that increase serotonin activity including SSRIs), betablocker, alpha-adrenergic agonist (clonidine), dopamine partial agonist or tricyclic antidepressant treatment
- Anticholinergic agents used to treat conditions such as, but not limited to, hyperhidrosis, asthma, incontinence, gastrointestinal cramps, and muscular spasms by any route of administration (e.g., intravenous, oral, inhaled, topical, etc.)
- Any topical prescription treatment for hyperhidrosis
- Any oral or topical homeopathic or herbal treatment (i.e., alternative therapies such as sage tablets, chamomile, valerian root and St. John's Wort)
- Use of potent inhibitors of cytochrome P450 CYP3A (including grapefruit juice) & CYP2D6 and transporter inhibitor (OCT2/MATE1/MATE2). Use of topical antifungal medications is permitted if not applied in the treatment area.

6.14 Prevention of Pregnancy during the Study

6.14.1 Instructions for Female Subjects

Females must agree to pregnancy testing and use a medically acceptable method of contraception while receiving study drug. Acceptable contraceptive methods include the following:

- Abstinence for the duration of the study or where partner is sterile (e.g., vasectomy) is acceptable form of contraception;
- Hormonal contraception, including oral, injectable, or implantable methods started ≥2 months prior to screening; OR
- Two forms of non-hormonal contraception, including IUD (≥1-week status post placement) and properly used barrier methods (e.g., male or female condoms, cervical cap/diaphragm, spermicidal agents).

6.15 Lifestyle Guidelines

Not applicable

7 STUDY VISITS

The procedures and assessments to be performed at each visit are indicated in the SCHEDULE OF ACTIVITIES. The timing of each visit (while on treatment) is relative to Screening/Enrollment (Week 0 [Day 1]) when enrollment occurs. An estimated time for the conduct of each visit is provided as a guide only to the study site personnel and study subject (guardian/caregiver) for planning purposes. Note: it will not be considered a departure from the protocol if the visit length is shorter or longer than anticipated.

7.1 Screening/Enrollment (Week 0 [Day 1])

The final visit (Day 8/Visit 4) of Study BBI-4000-CL-105 and Screening/Enrollment (Week 0 [Day 1]) of this long-term extension Study BBI-4000-CL-108 will take place simultaneously. Therefore, procedures required under Study BBI-4000-CL-105, which are also required under the extension study will be recorded. The length of the additional time to complete additional activities associated with Screening/Enrollment visit is approximately 1.5 hours.

- Informed Consent Process
    - The parent(s)/legal guardian (s) must provide written informed consent prior to any study procedure being done; and
    - If able, the subject must provide assent to participate in the study.
- Interview
    - Evaluate Inclusion/Exclusion criteria\
- Assessments
    - Obtain and record vital signs
    - Record local tolerability assessment
- Sample Collection
    - Collect blood samples for safety laboratory testing (hematology and chemistry), and pregnancy testing (as applicable)
    - Collect urine sample for urine laboratory testing, routine urinalysis and pregnancy testing (females only)
- Instructions
    - Inform parent/guardian (caregiver) and subject that dosing will occur in the evening at approximately the same time before bedtime.
    - One pump container of sofpironium bromide gel, 15%, enough for 1 month of dosing, and one dosing diary card will be dispensed.
    - Review instructions for study drug application and use of the dosing diary card.
    - Study site personnel will prime the sofpironium bromide gel, 15% pump container with five (5) sequential actuations.
    - Weigh the sofpironium bromide gel, 15% primed pump container with cap.

- Provide study product application instruction brochure to subject (parent/guardian).
- Provide gloves if study drug to be dispensed by a parent/guardian.
- The next visit will be scheduled.

7.2 Treatment: Week 4 (Day 28 [±3 days]) through Week 24 (Day 168 [±5 days])

Visits will occur at Week 4 (Day 28 [±3 days]), Week 8 (Day 56 [± 5 days]), Week 12 (Day 84 [±5 days]), Week 16 (Day 112 [±5 days]) and Week 20 (Day 140 [±5 days]). It is estimated that each visit will take approximately 1.5 hours.

- Interview
  - Update medications since last visit
  - Assessment of AEs
- Assessments
  - Obtain and record vital signs
  - Perform an abbreviated physical examination
  - Complete an ECG at Week 4 (Day 28 [±3 days])
  - HDSM-Ax (or HDSM-Ax, Child) and PGI-S assessment (completed by the subject)
  - Application site (axillae) tolerability assessment (completed by subject prior to Investigator assessment, and Investigator assessment)
- Review dosing diary card (compliance check) at each visit.
- Sample Collection
  - Collect blood sample for safety laboratory testing and PK and urine sample for urine laboratory testing at Week 4 (Day 28 [±3 days]);
  - Collect urine sample for pregnancy testing (as applicable) at all visits
- Instructions
  - Collect subject's previously dispensed sofpironium bromide gel, 15%, pump container from prior visit. Record weight of container with cap.
  - Collect subject's completed dosing diary card from prior visit and review for compliance.
  - Prime and weigh to-be-dispensed sofpironium bromide gel, 15% pump container with cap prior to dispensing.
  - Dispense one sofpironium bromide gel, 15%, pump container and one dosing diary card.
  - Provide gloves if study drug to be dispensed by a guardian (caregiver).
  - Remind subject to return sofpironium bromide gel, 15% pump container and dosing diary card for the next study visit.
  - The next visit will be scheduled.

7.3 End of Treatment/Early Termination: Week 24 (Day 168 [±5 days])

It is estimated that each visit will take approximately 1.5 hours.

- Interview
    - Update medications since last visit
    - Assessment of AEs
- Assessments
    - Obtain and record vital signs
    - Perform an abbreviated physical examination
    - Complete an ECG
    - HDSM-Ax (or HDSM-Ax, Child) and PGI-S assessment (completed by the subject)
    - PGI-C assessed
    - Application site (axillae) tolerability assessment (completed by subject prior to Investigator assessment, and Investigator assessment)
- Review dosing diary card (compliance check)
- Sample Collection
    - Collect blood sample for safety laboratory testing and PK and urine sample for urine laboratory testing
    - Collect urine sample for pregnancy testing
- Instructions
    - Collect subject's previously dispensed sofpironium bromide gel, 15%, pump container from prior visit. Record weight of container with cap.
    - Collect subject's completed dosing diary card from prior visit and review for compliance.
    - The next visit will be scheduled.

7.4 End of Study: Week 26 (Day 182 [±5 days])

The end of study visit will occur at Week 26, approximately 2 weeks after the last application of study drug. It is estimated that this visit will take approximately 1.5 hours to complete.

- Interview
    - Update medications since last visit
    - Assessment of AEs
- Assessments
    - Perform an abbreviated physical examination
    - Obtain and record vital signs

- Complete an ECG if clinically significant abnormalities noted at Week 24 (Day 168 [±5 days])

- Sample Collection
  - Collect blood samples for safety laboratory testing and urine sample for urine laboratory testing if clinically significant abnormalities noted at Week 24 (Day 168 [±5 days])

7.5 Unscheduled Additional Visit(s)

An unscheduled visit may occur between visits to evaluate AEs, as applicable. An additional unscheduled visit will be scheduled every 7 to 14 days in order to follow-up on unresolved AEs or laboratory abnormalities that were still present at the final Visit 8 (Week 26).

8 INVESTIGATIONAL PRODUCT

8.1 Formulation, Packaging and Labelling

8.1.1 Formulation

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

8.1.2 Packaging and Labeling

Study drug is packaged in a white colored, metered pump container. One pump container is packaged in a carton with 2 applicators. The total gel volume in each pump container is approximately 50 mL (~43 g). The gross weight of each full container at baseline is approximately 78 to 84 grams. One full pump actuation delivers ~0.67 mL of the gel formulation. Therefore, each pump container is sufficient for 30 days of dosing per protocol instructions. The external carton will be labeled with “Caution: New Drug – Limited by Federal Law to Investigational Use”.

8.2 Storage

When stored in the clinic, the study drug 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. 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.

When study drug is stored in the subject’s home, it should be kept out of the reach of children except when used under supervision by the guardian/caregiver. The study drug contains alcohol and is flammable. The subject/caregiver should not store the product near open flames or in an area exposed to extreme heat.

8.3 Dispensing

One pump container is packaged in a carton with 2 applicators and will be dispensed at Week 0 (Day 1), Week 4 (Day 28 [±3 days]), Week 8 (Day 56 [±5 days]), Week 12 (Day 84 [±5

days]), Week 16 (Day 112 [±5 days]), and Week 20 (Day 140 [±5 days]). Gloves will be provided if study drug to be dispensed by a guardian (caregiver).

8.4 Dosing

The subject and parent(s)/guardian(s) will be reminded of the proper application of the study drug and that the drug will be applied before bedtime (Refer to Appendix C).

8.5 Compliance

The subject and/or the parent(s)/guardian(s) will record that the study drug was applied to each axilla (right and left) and when the subject applied the study drug in the dosing diary card. The site personnel will review the dosing diary card and weigh the pump container with cap on, at Week 4 (Day 28 [±3 days]), Week 8 (Day 56 [±5 days]), Week 12 (Day 84 [±5 days]), Week 16 (Day 112 [±5 days]), Week 20 (Day 140 [±5 days]), and Week 24 (Day 168 [±5 days]).

8.6 Study Drug Accountability

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by regulatory authorities at any time. Study drug will be received and dispensed by the designated study staff. All study drug will be accounted for on the study drug inventory/accountability log and will include:

- Subject ID
- Date/time dispensed
- Amount dispensed
- Amount remaining in inventory

Damaged or lost study drug will also be accounted for and recorded in the drug accountability records.

At completion of the study, the Investigator (or designee) is responsible for returning all unused study drug and used study drug containers to the Sponsor (or designee) and must verify that no supplies remain in the investigator's possession.

8.7 Blinding

Not applicable as this is an open-label study.

8.8 Breaking the Study Blind

Not applicable

9 PROTOCOL VIOLATIONS

A protocol violation occurs when the study subject, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, study subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Dosing error

- Out of window blood sample collection or visit

Failure to comply with GCP guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a study subject or if data analysis will be censored.

When a protocol violation occurs, it will be discussed with the Investigator, and the details will be documented and reviewed by the Sponsor representative and the Investigator. A copy of such documentation will be filed in the site's regulatory binder and in the Sponsor's files and may be reported to the IRB/IEC as applicable.

10 ADVERSE EVENTS

10.1 Safety Evaluations

The Investigator is responsible for the appropriate medical care and the safety of subjects who have entered this study. Safety will be assessed by physical examinations, laboratory tests, and measurement of vital signs assessed as indicated throughout the study schedule. Clinically significant changes in these parameters may be captured as AEs.

The Investigator must document any AE experienced by subjects who have entered this study and report all SAEs to the Sponsor (see Section 10.3.1). Contact information for the Sponsor's medical monitor is provided on the protocol covering page.

10.2 Adverse Events

10.2.1 Definition of Adverse Events

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

- An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
- A suspected drug-related adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

The following information should be considered when determining whether to classify a test result, medical condition, or other incident as an AE:

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

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

10.2.2 Documentation and Monitoring Adverse Events

All AEs encountered during the clinical trial following subject consent through the last study visit will be recorded on the appropriate Adverse Events case report form (eCRF).

Special considerations:

- Elective procedures or routinely scheduled treatments are not considered AEs. However, an untoward medical event occurring in association with a prescheduled elective procedure should be recorded as an AE.
- A baseline condition is not considered an AE unless the condition worsens following study drug administration.
- Death itself is not considered an AE; it is, instead, the outcome of an AE.
- SAEs that are considered related (i.e., determined to be possibly, probably, or definitely related) to sofpironium bromide by the Investigator or Sponsor should be followed until the event resolves or stabilizes (see Section 10.3.1).

10.2.3 Assessment of Adverse Events

For each reported AE, the start and resolution dates, intensity, seriousness (i.e., whether the event meets the definition of an SAE [Section 10.3.1]), relationship of the event to the study drug, action taken regarding study drug, and outcome of the event will be documented on the eCRF.

Intensity

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

Severity	Grade	Description
Mild	1	Awareness of sign or symptom, but easily tolerated
Moderate	2	Discomfort enough to cause interference with usual activity
Severe	3	Incapacitating with inability to work or do usual activity

Note: a severe AE is not necessarily serious.

Relationship

The relationship of a reported AE to study drug should be assessed using the guidelines presented in the following table.

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

Outcome

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

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

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

Action Taken with Study Drug

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

- None
- Drug withdrawn
- Drug interrupted
- Unknown
- Not applicable

- Other (specify on eCRF)

10.3 Serious Adverse Events

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

10.3.1 Definition and Reporting Procedures

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

Fatal:	The AE resulted in death.
Life Threatening:	The AE placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not serious AEs by this criterion. Hospitalizations or prolonged hospitalizations for scheduled therapy need not be captured as SAEs.
Disabling/Incapacitating:	Resulted in a substantial and permanent disruption of the patient's ability to carry out activities of daily living.
Congenital Anomaly or Birth Defect:	An adverse outcome in a child or fetus of a patient exposed to the study drug or study treatment regimen before conception or during pregnancy.
Medically Significant:	The AE did not meet any of the above criteria but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.

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

Additional updates from the Investigator may be necessary as more information becomes available on the SAE, and all treatment-related SAEs will be followed until the acute event has resolved or stabilized, even if the subject discontinues study participation prior to the SAE resolution. Any new information or follow-up information pertaining to previously reported SAEs will be reported to the Sponsor within 24 hours of becoming aware of the new or follow-up information. The new or follow-up information should be faxed to the Sponsor at 1-866-666-7392 or emailed to safety@brickellbio.com.

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

10.3.2 Reporting Serious Adverse Events to Regulatory Agencies

The Sponsor will determine which SAEs qualify for expedited reporting to regulatory agencies. SAEs that qualify for expedited reporting will be submitted to regulatory agencies in accordance with applicable federal regulations.

10.4 Follow-up of Adverse Events and Laboratory Test Abnormalities

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

10.5 Pregnancy Reporting

10.5.1 Definition of Female of Childbearing Potential

For purposes of this study, all female subjects are considered of childbearing potential.

10.5.2 Testing and Acceptable Methods of Birth Control

Females must agree to periodic pregnancy testing and use a medically acceptable method of contraception while receiving protocol-assigned study drug. Refer to Section 6.14.1 for additional information.

10.5.3 Time Period for Collecting Pregnancy Information

Females of child bearing potential 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.

10.5.4 Action to be Taken if Pregnancy Occurs

If following initiation of investigational product, it is subsequently discovered that a trial subject was pregnant or may have been pregnant at the time of investigational product exposure, the Investigator must immediately notify the Medical Monitor of this event and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to the Medical Monitor by fax to 1-866-666-7392 or email at safety@brickellbio.com. The Investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

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

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

11 DATA ANALYSIS AND STATISTICAL METHODS

11.1 Sample Size Determination

A sample size of twenty-four (24) subjects is based on the maximum planned enrollment under Study BBI-4000-CL-105.

11.2 Analysis Populations

Two populations will be used for analysis: Safety and PK. The definition of these two populations follows:

- **Safety Population**: All enrolled subjects who applied at least one dose of study drug and have at least one post-baseline safety assessment.
- **Pharmacokinetic Population:** All enrolled subjects who applied at least one dose of study drug and have at least one quantifiable PK sample for analysis.

11.3 Statistical Analysis

11.3.1 General Statistical Methodology

- Baseline is defined as the last assessment prior to the first application of study drug on Day 1 under Study BBI-4000-CL-105.
- All statistical processing will be performed using Statistical Analysis System (SAS®) unless otherwise stated.
- Continuous data will be summarized using descriptive statistics (number of values, mean, standard deviation, median, minimum and maximum). Categorical data will be summarized using frequency tables (frequencies and percent).
- A SAP, describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to locking the database. The SAP will contain any modifications to the analysis plan presented below.

11.3.2 Demographics, Baseline Characteristics, Medical History, Hyperhidrosis History, and Concomitant Medications

Demographic data, baseline characteristics, medical history including history of axillary hyperhidrosis, and prior and concomitant medications will be summarized using descriptive statistics.

11.3.3 Treatment Compliance

The subject or parent(s)/guardian(s) will record the date and time of all applications made to the right and left axilla or missed applications in the dosing diary card. Subject compliance during the overall treatment period and by visit will be summarized.

11.3.4 Drug Exposure

Amount of study drug (weight) and the number of days of study drug application will be summarized.

11.4 Primary Analysis

11.4.1 Safety

Safety evaluations will consist of AEs, local application site tolerability, vital signs, laboratory measurements (hematology, chemistry, and urinalysis, and pregnancy testing), ECGs and physical examinations. Full details will be specified in the SAP. A general description of the planned analysis is as follows:

- Adverse Events:
    - Adverse events will be descriptions will be mapped to standard terms, i.e., MedDRA System Organ Class and Preferred Term.
    - Adverse events that occurred during the screening period will be listed separately and will not be included in the AE tabulations.
    - Adverse events that start on or after first dose will be considered a TEAE. At each post-baseline visit, the number and proportion of subjects reporting any given TEAE will be tabulated by severity; each subject will be counted only once according to the worst severity reported up to the current visit. Separate tables will be constructed for (a) all reported TEAEs, (b) protocol treatment related TEAEs, (c) serious TEAEs, and (d) TEAEs leading to protocol treatment discontinuation.
- At each visit, local tolerability (burning, itching, stinging, scaling, and erythema at either axilla) will be described by severity as defined in Appendix F.
- Vital signs will be summarized similarly as for laboratory parameters but without shift tables.
- Laboratory parameters will be descriptively summarized (mean, SD, median, minimum, maximum) for values at each visit and for changes from baseline at each subsequent visit. In addition, at each post baseline visit, parameter status (low, normal, high) will also be summarized as shift tables vs. baseline status.
- Descriptive statistics and/or frequency tables will be prepared as appropriate for physical examinations, and ECG (HR, RR, QTcF, PR, and QRS) parameters
- Concomitant medications will be mapped according to the World Health Organization Drug Dictionary and will be presented in data listings.

11.4.2 Pharmacokinetics

Plasma concentrations of sofpironium and BBI-4010, will be determined using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) analytical methods. The lower limit of quantification (LLQ) of the assay in plasma is 0.0555 ng/mL for both sofpironium and BBI-4010. Specifics of the analytical procedures will be provided in separate bioanalytical documentation.

Individual plasma C_{trough} values of sofpironium and BBI-4010 will be summarized descriptively using the arithmetic mean, SD, CV (%), median, minimum and maximum. Mean (±SD) C_{trough} values will also be presented graphically by week to assess exposure, accumulation and steady state

Additional details regarding PK analysis will be provided in the SAP.

11.5 Exploratory Analysis

- Descriptive summaries will be provided for HDSM-Ax and HDSM-Ax, Child, Summary Questions (No. 4 and No. 5) and PGI-S. Mean changes from baseline and observed values will be summarized by time point. The SAP will contain full details.
- For HDSM-Ax and HDSM-Ax, Child, the mean of the items in Section No. 1, No. 2, and No. 3 will be calculated for every subject at each time point. The mean will be derived by taking the total score and dividing it by the number of questions answered. Subjects must answer ≥6 of the 11 sub-items to be evaluable for HDSM-Ax or HDSM-Ax, Child total score. Observed values and changes from baseline at each time point will be summarized and plotted over time using descriptive statistics.
- For the HDSM-Ax or HDSM-Ax, Child Summary Questions (No. 4 and No. 5), the score for each question, will be reported for every subject at every visit and summarized and plotted over time using descriptive statistics.
- For PGI-S, the score will be reported for every subject at every visit and summarized and plotted over time using descriptive statistics.
- For PGI-C, the score will be reported for every subject at Week 12 and Week 24 (EOT) and summarized and plotted over time using descriptive statistics.

Missing data will not be imputed for any analyses.

11.6 Interim

No interim analyses are planned.

12 DATA COLLECTION, RETENTION AND MONITORING

12.1 Data Collection Instruments

The Investigator will maintain adequate and accurate source documents designed to record all observations and other pertinent data for each study subject treated with the test article. Study personnel at each site will enter data from source documents corresponding to a study subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

Study subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee) but will be identified by a site number and study subject number.

When changes or corrections are made in the eCRF, the EDC systems will maintain an audit trail of the person making the changes, the date and time of the change and the reason for the change. Only individuals listed on the Delegation of Responsibilities Log with responsibility for eCRF completion may make entries in the eCRFs.

The Investigator is responsible for all information collected on study subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. Copies of final completed eCRFs will be provided on a compact disk or other similar media for archiving at the study site following database lock and at or prior to study closure.

12.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

12.2.1 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

12.2.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential. Data should be entered onto the eCRF approximately no later than 72 hours after the visit has taken place.

12.2.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of the MedDRA for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

12.2.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the uploaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries. The eCRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

12.3 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

12.4 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each study subject must be maintained that includes the

signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that study subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

All study documents (patient and subject files, signed informed consent forms, copies of eCRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

12.5 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor (or designee) according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6 (R2)). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

12.6 Subject Confidentiality

In order to maintain study subject confidentiality, only a site number, and subject number will identify all study subjects on eCRFs, blood samples, and other documentation submitted to the Sponsor. Additional study subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

12.7 Retained Blood Samples

Blood samples collected during the study for pharmacokinetic analysis may be retained for future testing as necessary. Study subject's confidentiality will be maintained and only the site and study subject number will identify the sample. No other linked or identifying information is maintained by the Sponsor.

13 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312 Subpart D).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. All study records will be kept in a locked secured area. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

13.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor or Sponsor designee. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to study subjects/patients. A protocol amendment intended to eliminate an apparent immediate hazard to study subjects/patients may be implemented immediately, provided the IRBs are notified within five working days.

13.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent forms [parental consent and assent collectively referred to as "consent"] will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning subject/patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subject or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the subjects/patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.3 Informed Consent Form – General Provisions

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. Also refer to Protocol Section 6.1.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent/assent forms generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Council on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form and Assent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each study subject or the subject's legally authorized representative prior to entering the study subject into the trial and conducting any Screening visits. Information should be given in both oral and written form and study subjects (or their legally authorized representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local

IRB/IEC, assent from the study subject will also be obtained. If a study subject is unable to sign the ICF and the HIPAA authorization, a legal representative may sign for the study subject. A copy of the ICF (and assent) will be given to the study subject or legal representative of the study subject and the original will be maintained with the study subject's records.

13.4 Publications

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

13.5 Clinical Trials Registration

If the study falls within the requirements of an "applicable clinical trial" (ACT) as defined in section 402(j) of the Public Health Service Act, the study will be registered by the Sponsor (or designee) on ClinicalTrials.gov. The name of the Investigator or investigational site may be included under Contacts and Locations, as required.

14 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the referenced investigational drug at any time.

If the study is prematurely terminated or discontinued, the Sponsor, or designee, will promptly notify the Investigator. After notification, the Investigator must contact all participating study subjects within 5 business days. As directed by the Sponsor all study materials must be collected and all eCRFs completed to the greatest extent possible.

15 REFERENCES

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APPENDIX A HDSM-AX, CHILD (≥9 TO <12 YEARS OF AGE)

HDSM-AX CHILD (VERSION 28 FEB 2018)

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

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

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

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

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

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

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

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

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

0 None of the time
1 A little of the time
2 Some of the time
3 Most of the time
4 All of the time

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

0 I did not have underarm sweating
1 I had a tiny amount of underarm sweating
2 I had some underarm sweating
3 I had a lot of underarm sweating
4 I had a great amount of underarm sweating

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

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

☐ None
☐ Mild
☐ Moderate
☐ Severe
☐ Very severe

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

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

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

APPENDIX B HDSM-AX (≥12 YEARS OF AGE)

HDSM-Ax Version 1.3

Hyperhidrosis Disease Severity Measure--Axillary©

(HDSM-Ax)

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

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

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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 caused by underarm sweating?	0	1	2	3	4
b) Underarm sweating for no apparent reason?	0	1	2	3	4

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

	I did not experience this	Mild	Moderate	Severe	Very severe
a) Underarm sweating when you felt nervous, stressed or anxious?	0	1	2	3	4
b) Damp or wet clothing caused by underarm sweating?	0	1	2	3	4
c) Underarm sweating after little or no physical exercise?	0	1	2	3	4
d) Underarm wetness?	0	1	2	3	4
e) Underarm sweating for no apparent reason?	0	1	2	3	4
f) Underarm sweating that was unmanageable?	0	1	2	3	4
g) Underarm sweating when you were cool?	0	1	2	3	4

HDSM-Ax Version 1.3

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

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

0 None of the time
1 A little of the time
2 Some of the time
3 Most of the time
4 All of the time

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

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

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

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

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

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

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

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

APPENDIX C STUDY DRUG APPLICATION AND SUBJECT INSTRUCTIONS AND DOSING DIARY CARD

- The study drug will be applied every day, at home before bed, at about the same time.
- The study drug will be applied as follows:

Steps

1. Expose the underarm areas and ensure they are dry. Do not wash the underarm areas for at least 30 minutes prior to application.
2. If caregiver will be applying the gel, gloves (provided) should be worn while dispensing the gel and when washing applicator.
3. Hold the plastic applicator between the index and middle fingers and the thumb of the left hand. Carefully, by applying consistent pressure to the actuator with an index finger, dispense the gel of ONE FULL actuation onto the dome of the white plastic applicator.
4. Immediately apply study drug to the right underarm area.
5. Distribute all the gel expressed using the plastic applicator in a way that covers all the underarm area by gently applying a layer of the product.
6. Repeat steps 3, 4 and 5 for the left underarm. If self-applying use the right hand.
7. Wash both hands and the plastic applicator thoroughly for about 2 minutes.
8. Allow the study drug to dry for 5 minutes before putting any clothes on the upper body.
9. Record in the dosing diary card each time (date and time) the study drug is applied and check off that it was applied to the right and left underarm.

Important information:

- Avoid touching the underarm.
- 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 in the morning then it should be at least 30 minutes before study product application. Ensure the underarm areas are dry prior to application of the study product.
- Subjects should not apply any other product to the axillary area (including deodorant) for at least 8 hours after study product application.
- The subject/caregiver should use the applicator provided to avoid contact with skin of the hands. Gloves will be provided and should be worn if gel applied by the caregiver. 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/caregiver should avoid fire, flames or smoking during the application and until the gel has dried. The subject should not expose the container to fire, flames or extreme heat.

SUBJECT/CAREGIVER 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/your child participates in this study, you/your child will be expected to:

- Follow the instructions that are given and come to the study center for visits with the study doctor or study staff or allow a visiting nurse to come to your/your child's home or school to complete the study visit.
- Record in the dosing diary card each time (date and time) the study drug is applied. Check off that the study drug was applied to your/your child's right and left underarm.
- DO NOT apply the study drug before a study visit (or when the study nurse will be visiting).
- Tell the study doctor or study staff about any changes in your/your child's health or the way you/your child are feeling.
- Tell the study doctor or study staff if you/your child want to stop being in the study at any time.
- Do not shower, shave, or wash the underarm area within 30 minutes of study drug application and for at least 8 hours after study drug application.
- Be careful not to touch the eyes or mouth with the gel or with your hands while applying the gel.
- You/your child must practice the required method of birth control throughout the entire study if you/your child are able to become pregnant.
- You/your child must not breastfeed while you/your child are in the study (for applicable females).
- Use a loose T-shirt or similar clothing item and avoid touching the underarm area.
- Do not start any new medications or change your/your child's medications without approval from the study doctor.
- Do not allow access to the study drug assigned to you/your child to anyone beside the study staff.
- Store the study medications according to the instructions on the label.

IMPORTANT:

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

Bring the previously dispensed Study Drug pump container to every clinic visit along with the completed dosing diary card.

Dosing Diary Card BBI-4000-CL-108
(EXAMPLE INFORMATION TO BE COMPLETED BY SUBJECT/PARENT/GUARDIAN)

	Apply 1 full pump to each axilla before bed. Check areas applied and enter time application complete						
	Day	**Date (dd/mm)** **Year_____**	**Time of Dosing (PM)**	**Right Axilla** ☑	**Left Axilla** ☑	**Comments**	**Parent/ Guardian Dose Verification (signature)**
Week 1	1		:				
	2		:				
	3		:				
	4		:				
	5		:				
	6		:				
	7		:				
Week 2	8		:				
	9		:				
	10		:				
	11		:				
	12		:				
	13		:				
	14		:				

Bring the previously dispensed Study Drug pump container to every clinic visit along with the completed dosing diary card.

APPENDIX D EXAMPLES OF POTENT INHIBITORS CYP3A AND CYP2D6

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

Example Potent Inhibitors of CYP2D6		
bupropion	fluoxetine	paroxetine
quinidine	terbinafine	

Also refer to FDA reference link "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers"
[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2]
Concomitant medication restrictions (6.13.2)

APPENDIX E EXAMPLES OF POTENT INHIBITORS OF OCT-2/MATE1/MATE2 TRANSPORTERS

Example Potent Inhibitors of OCT2		
Cimetidine		

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

Also refer to FDA reference link "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers"
[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2]
Prohibited medications (6.13.2)

APPENDIX F APPLICATION SITE TOLERABILITY ASSESSMENTS

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

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

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

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

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