BrickellBiotech

Statistical Analysis Plan

Protocol BBI-4000-CL-108

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

Version/Date	0 (Original) 21 September 2018
Sponsor	Brickell Biotech Inc. 5777 Central Ave., Suite 102 Boulder, CO 80301

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TABLE OF CONTENTS

ABBREVIATIONS

Abbreviations	Definitions
AE	Adverse event
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CSR	Clinical study report
C_{trough}	Trough concentration
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of treatment
EOS	End of study
HDSM-Ax	Hyperhidrosis Disease Severity Measure-Axillary
HDSM-Ax, Child	Hyperhidrosis Disease Severity Measure-Axillary, Child
hr, h, hrs	Hour(s)
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minutes
mL	Milliliter(s)
N	number
PGI-S	Patient Global Impression of Severity
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetics
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SRC	Study Review Committee
TEAE	Treatment-emergent adverse event
US	United States of America

1 REVISION HISTORY

Revision No./ Date [1]	Author of Revision [2]	Section(s) Modified	Description and/or Reason(s) for Revision

[1] Update the last revision dates on the cover page and the footer
[2] Provide first initial and last name

2 INTRODUCTION

2.1 Background

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

2.2 Rationale

The pediatric pharmacokinetic (PK) 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 (QD) sofpironium bromide gel, 15% treatment for up to 24 weeks. 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.

This Statistical Analysis Plan (SAP) is based on the protocol for Study BBI-4000-CL-108, Version 0 (Original), dated 21 September 2018.

3 STUDY OUTLINE

This multicenter, open-label extension study will evaluate the long-term safety, tolerability, and PK 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 a 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).

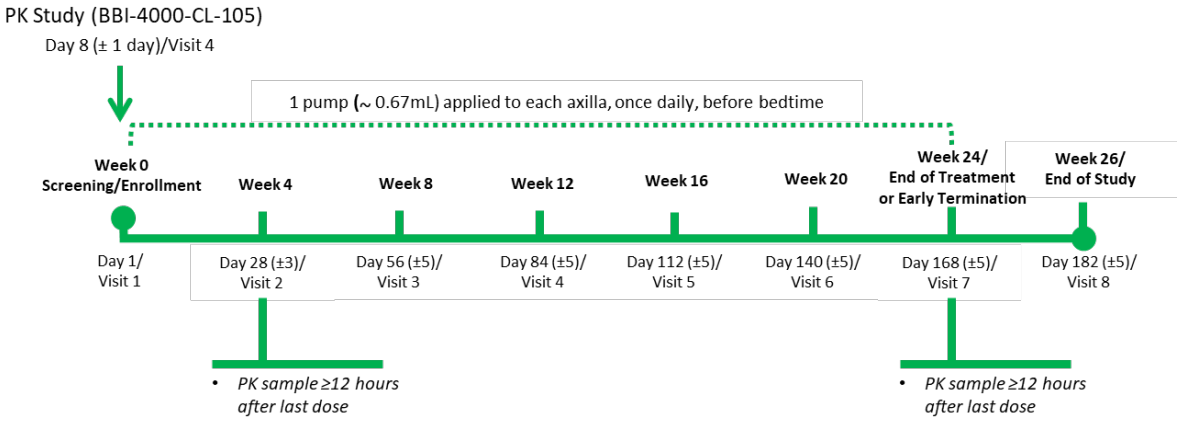
Vital signs, review of concomitant medications, assessment of adverse events (AEs), completion of patient-reported outcomes (Hyperhidrosis Disease Severity Measure-Axillary [HDSM-Ax] and Hyperhidrosis Disease Severity Measure-Axillary, Child [HDSM-Ax, Child] and Patient Global Impression of Severity [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. Electrocardiograms (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 EOT at Week 24 (Day [168 ±5 days]), the subject will also complete the Patient Global Impression of Change (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, and 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 SCHEDULE OF ACTIVITIES

Description With Protocol Reference	**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	
PK sampling Refer to Section 6.12.5	X [b]	X [c]					X [c]	

Description With Protocol Reference	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**
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 Study BBI-4000-CL-105 will be carried over to the current study.
[b] Data collected at EOT (Day 8 [±1 day]) under Study 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.

5 STUDY DURATION

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 (Visit 1 [Day 0]) and EOT visit of Study BBI-4000-CL-105 (Day 8 [±1 day]) will be conducted simultaneously.

6 STUDY POPULATON

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

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Objectives

7.1.1 Primary Objectives

7.1.1.1 Safety

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

7.1.1.2 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, QD for up to 24 weeks.

7.1.2 Exploratory Objectives

- To assess the effect of topically applied sofpironium bromide gel, 15% on HDSM-Ax and 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 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 PGI-C in pediatric subjects, ≥9 to ≤17 years of age, with axillary hyperhidrosis.

7.2 Endpoints

7.2.1 Primary Endpoints

7.2.1.1 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, physical examination, 12-lead ECGs and vital signs
- Proportion of subjects who discontinue treatment due to an AE

7.2.1.2 Pharmacokinetics

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

7.2.2 Exploratory Endpoints

- Change of HDSM-Ax (≥12 years of age) or HDSM-Ax, Child (≥9 to <12 years of age) from baseline to EOT
- 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 EOT
- PGI-C at Week 12 (Day 84) and EOT

7.3 Study Assessments

7.3.1 Safety

- Adverse events at all visits
- Local application site tolerability assessments (including burning, itching, stinging, scaling and erythema) at all visits through Week 24 [Day 168] and Week 26 (Day 182), if applicable
- Vital signs (heart rate [HR], blood pressure, 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)

7.3.2 Pharmacokinetics

- Plasma samples will be collected ≥12 hours after the last dose on 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]).

7.3.3 Efficacy

- HDSM-Ax or HDSM-Ax, Child as measured at all visits through and including Week 26 (Day 182 [±5 days]).
- 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)
- PGI-S, as measured by the subject at all visits through and including Week 26 (Day 182 [±5 days]).
- PGI-C as measured by the subject at Week 12 (Day 112 [±5 days]) and Week 24 (Day 168 [±5 days]).

8 DOSING AND COMPLIANCE

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.

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]).

9 BREAKING THE BLIND

Not applicable as this is an open-label study.

10 STUDY REVIEW COMMITTEE

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.

11 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.

12 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

12.1 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.

12.2 Interim Analysis

No interim analyses are planned.

12.3 General Considerations for Analysis

12.3.1 Safety and Efficacy Analysis

- The Safety population will be used for evaluation of safety and efficacy parameters.
- Analyses of safety and efficacy data will be performed in Statistical Analysis System (SAS) software version 9.2 or higher (SAS Institute Inc., 2008).
- The final analysis will be conducted after all subjects have completed the study and the database is locked. Listings will report all data collected in the database.
- If a data table is sparse, only a listing will be presented. Unless otherwise stated, all listings will be sorted by subject number and visit date. Continuous variables will generally be summarized using means, medians, standard deviation (SD), minimum, and maximum. Discrete variables will be summarized by frequency and percentages.
- Summary tables will indicate the number of subjects with complete data for each measurement, event, or outcome.
- Data will be summarized in plots organized by time point and over time.
- For multiple or repeated assessments for the same visit, the latest assessment will be included in the summary tables.
- Summary tables will only include data from scheduled visits.
- Data from unscheduled visits will be included in the listings.
- If additional analyses are required to supplement the planned analyses, they may be performed and will be identified in the appropriate section of the clinical study report

(CSR). Any substantial deviations from the planned SAP will updated in the SAP and approved.

12.3.2 Pharmacokinetics

- The PK population will be used for evaluation of PK parameters.
- All plasma PK parameter calculations (C_{trough} values) will be performed using actual time points (actual date and time of each blood draw) calculated relative to the time of study drug administration.
- Graphical comparison of C_{trough} values (collected ≥12 hours after the prior dose) on Week 0 (Day 1), Week 4 (Day 28 ±3 days), and Week 24 (Day 168 [±5 days]) will be used to assess steady state levels.
- All descriptive analyses and generation of tables, listings and figures, will be performed using a validated installation of Phoenix WinNonlin® version 8.0 (Pharsight, Cary, North Carolina, USA) as part of a 21 CFR Part 11 compliant database system (Pharsight Knowledgebase Server "PKS").
- The final analysis will be conducted after all subjects have completed the study, all PK samples collected, have been analyzed, and the database is locked.
- Subject demographics, baseline characteristics, disposition, dosing dates and dosing times, and compliance data necessary to support analysis of PK, will be imported (SAS datasets) from the clinical safety and efficacy database (eCRF data).
- If additional analyses are required to supplement the planned PK analyses, they may be performed and will be identified in the appropriate section of the CSR. Any substantial deviations from the planned SAP will updated in the SAP and approved.

12.3.3 Handling of PK Concentration Values Below the Limit of Quantification

The lower limit of quantification of the assay in plasma is 0.0555 ng/mL for both sofpironium and BBI-4010. Concentrations that are reported as below the limit of quantitation will be set to 0 for the calculation of the descriptive statistics for the drug concentration summary.

12.3.4 Handling of Missing PK Sampling or Concentration Data

Missing sampling or concentration values will not be imputed but left missing in the calculation of mean concentrations. Concentrations that are not reportable due to technical artifact or ambiguity will be treated as missing values. If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time will be used for the calculation of mean concentration.

12.3.5 Handling of PK Outliers

On a case by case basis, it may be necessary to exclude individual bioanalytical data from the calculation of mean concentrations because they are erroneous, abnormal or appear implausible to the pharmacokineticist in charge of the analysis. Any excluded data will be

flagged in the individual data listings. The reason for exclusion will also be documented. If the exclusion has a meaningful impact on the overall interpretation of the results, it will be discussed with the Sponsor.

12.3.6 Handling of Actual vs. Planned PK Sampling Timepoints

Actual post-dose time will be used in the Tables and Listings of individual C_{trough} values. The PK sample collection window (≥12 hrs from previous dose and prior to next dose) will be used to summarize descriptive statistics for C_{trough} values.

12.3.7 Handling of Individual PK Data and Summary Data Formats

The actual values as provided from the bioanalytical laboratory will be displayed as individual concentration-time listings. Drug concentrations will be used to calculate the mean using descriptive analysis. For summary tables, the descriptive statistics will be rounded to one more digit than the individual values for the arithmetic mean, SD, median and geometric mean, and to the same number of digits for the minimum and maximum values. The number of non-missing observations (N) will be reported as an integer number. The coefficient of variation (CV) (%) and geometric CV% will be reported as a percentage (CV*100) as an integer number.

12.4 Derived and Transformed Data

Baseline

The Baseline (Day 1, pre-dose) measurement of a variable is the latest non-missing measurement before the first dose of study drug in Study BBI-4000-CL-105

Age

Age (in completed years) will be calculated for each subject as:

Age (years) = (Date of Screening visit – Date of Birth + 1) / 365.25

12.5 Assessment Days and Windows

The listings will include all assessments. The following assessment windows are established:

- Visit 1: Screening/Enrollment (Week 0 [Day 1])
- Visit 2: Week 4 (Day 28 [±3 days])
- Visit 3: Week 8 (Day 56 [±5 days])
- Visit 4: Week 12 (Day 84 [±5 days])
- Visit 5: Week 16 (Day 112 [±5 days])
- Visit 6: Week 20 (Day 140 [±5 days])
- EOT/Early Termination Visit 7: Week 24 (Day 168 [±5 days])
- End of Study (EOS) Visit 8: Week 26 (Day 182 [±5 days])

12.6 Missing Safety and Efficacy Data

Adverse events recorded with ambiguous or missing start dates and times will be assumed to have started after the first dose of study drug on Day 1 of Study BBI-4000-CL-105. Consequently, such AEs will be included in all summaries of treatment-emergent adverse events (TEAE). Start and end dates and times for AEs will be listed as collected.

Where the start or end date of a concomitant medication is ambiguous or missing, the medication will be assumed to have been started before and continued after the first dose of study drug in Study BBI-4000-CL-105. That is, the medication will be listed as both prior and concomitant and included in the summary table of concomitant medications.

All other cases of missing or invalid data will be treated as missing and will not be imputed. Start and end dates for concomitant medications will be listed as collected.

12.7 Medication and Adverse Event Coding Dictionaries

- Concomitant medications are coded using the March 2018 version of the World Health Organization Drug Coding Dictionary (WHODD).
- Adverse events are coded using version 21.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

12.8 Protocol Deviations and Violations

Subject data will be examined for evidence of protocol deviations and violations in order to assess how well the investigators followed the protocol. A protocol deviation is a variation from processes or procedures defined in a protocol. Deviations usually do not preclude the overall evaluability of subject data and are often acknowledged and accepted in advance by the Sponsor. A protocol violation is a significant departure from processes or procedures that were required by a protocol. Violations often result in data that are not deemed evaluable for PK or efficacy analysis and may require that the subject(s) who violate the protocol be discontinued from the study.

A sponsor designee will perform a final review of the list of protocol deviations and violations prior to database lock and according to data available on the eCRF to adjudicate the categorization of the protocol deviations and violations.

13 STATISTICAL ANALYSIS

13.1 Baseline Parameters, Demographics, Medical History, Hyperhidrosis History, Concomitant Medications, Disposition and Drug/Alcohol Screening, and Pregnancy Testing

- The total number of subjects enrolled in the study.
- Subject demographics and baseline characteristics will include, date of birth, gender, race, ethnicity, height and weight, and age at onset and duration of hyperhidrosis, will be summarized and listed. Descriptive statistics (mean, SD, median, minimum, and maximum for numerical variables; count and percentage for categorical variables) will be presented where applicable.

- Subject medical, hyperhidrosis and medication history will be listed by MedDRA system organ class and preferred term (PT). A listing sorted by subject number, MedDRA system organ class and PT, and onset date will also be presented.
- Subject medication history will be mapped according to the WHODD.
- A listing of subject disposition will include start date and time of first study drug application in the extension study.
- The number of subjects who complete treatment (Day 168 [±5 days], EOT) will be summarized and listed.
- The number of subjects who complete study (Day 182 [±5 days], EOS) will be summarized and listed.
- The number of subjects who prematurely discontinue from the study and reason for discontinuation will be summarized and listed. The number of subjects who prematurely withdraw from study drug but remaining in the study will be summarized.
- Concomitant medications (start date on or after Day 1 of Study BBI-4000-CL-105) will be summarized using descriptive statistics.
- Use of concomitant medications (chronic medications or as needed medications e.g., acetaminophen, EMLA cream) are permitted during the screening and active study period (Day 1 through Day 168 [±5 days]) and will be recorded on the eCRF.
- Changes in concomitant medication usage will be recorded on the eCRF. If the reason for change is related to an AE, the event will be recorded in as an AE in the eCRF.
- Concomitant medications will be mapped according to the WHODD and will be presented in data listings.
- Drug and alcohol screen by visit will be listed.
- Pregnancy test (positive or negative) by visit will be listed.

13.2 Drug Exposure and Treatment Compliance

- Study drug applications made or missed, and location (right and left axilla) will be recorded on the dosing diary card and data will be entered in the eCRF. Study drug applications and application location by day and by visit will be summarized.
- Study drug compliance will be evaluated at each visit during the treatment period. 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]). Amount (by weight) of study drug used by visit and overall difference in weight between Day 1 and final dose application on Day 168 [±5 days], will be summarized.

13.3 Primary Analyses

13.3.1 Safety

Safety evaluations will consist of AEs, application site local tolerability, physical examinations, vital signs, ECGs, and laboratory measurements (hematology, chemistry, and urinalysis).

- Adverse events:
    - Adverse events 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 applicable visit, local tolerability (burning, itching, stinging, scaling, and erythema at either axilla) will be described by severity as defined in Appendix E. Subject and Investigator assessments will be included in separate tables and listings, with the count and percentage of subjects within each severity (maximum severity assessed at either axilla) presented by parameter and visit.
- 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, QTcF, PR, and QRS) parameters, and abnormalities (e.g., normal; abnormal, not clinically significant; abnormal, clinically significant).
- Concomitant medications will be mapped according to the World Health Organization Drug Dictionary (WHODD) and will be presented in data listings.

13.3.2 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

13.4 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.
- 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 each time point and will be summarized and plotted over time using descriptive statistics.
- For PGI-S, the score will be reported for every subject at each time point and will be 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 will be summarized and plotted over time using descriptive statistics.
- Missing data will not be imputed for any analyses.

14 REFERENCES

None

15 APPENDICES

15.1 Appendix A: Preliminary Table of Contents for Tables, Listings, Figures for Safety and Efficacy

Tables: Demographics, Baseline Characteristics, Analysis Populations/Subject Accountability, Medical History, Hyperhidrosis History, Concomitant Medications

Table 14.1.1 Analysis Populations / Subject Accountability

Table 14.1.2.1 Demographics, Baseline Characteristics - Safety

Table 14.1.2.2 Demographics and Baseline Characteristics- PK

Table 14.1.3 Medical History and Hyperhidrosis History – Safety

Table 14.1.4 Concomitant Medications - Safety

Efficacy Tables – Safety Population

14.2.1 Summary of HDSM-Ax and HDSM-Ax, Child Measurements and Changes from Baseline (All)

14.2.2 Summary of HDSM-Ax and HDSM-Ax, Child Anchors and Change from Baseline over Time (All)

14.2.3 Summary of PGI-S score and Change from Baseline over Time (All)

14.2.4 Summary of PGI-C score and Change from Baseline over Time (All)

Efficacy Figures – Safety Population

Figure 14.2.1 Mean Changes from Baseline Over Time in HDSM-Ax, Child and HDSM-Ax (All)

Figure 14.2.2 Mean Observed Values over Time in HDSM-Ax, Child and HDSM-Ax (All)

Figure 14.2.3 Mean Changes from Baseline Over Time in HDSM-Ax, Child and HDSM-Ax Anchors (All)

Figure 14.2.4 Mean Observed Values over Time in HDSM-Ax, Child and HDSM-Ax Anchors (All)

Figure 14.2.5 Mean Changes from Baseline Over Time in PGI-S (All)

Figure 14.2.6 Mean Observed Values over Time in PGI-S (All)

Figure 14.2.7 Mean Changes from Baseline Over Time in PGI-C (All)

Figure 14.2.8 Mean Observed Values over Time in PGI-C (All)

Safety Data – Safety Population

Displays of Adverse Events

Table 14.3.1.1 Incidence of Treatment Emergent Related Adverse Events by Severity

Table 14.3.1.2 Incidence of Serious Treatment Emergent Adverse Events by Severity

Table 14.3.1.2 Incidence of Serious Treatment Emergent Related Adverse Events by Severity

Abnormal Laboratory Value Listing (each Subject) – Safety Population

Table 14.3.4.1 Clinical Chemistry Laboratory Summary

Table 14.3.4.2 Clinical Chemistry Laboratory Values Shift Tables

Table 14.3.4.3 Hematology Laboratory Summary

Table 14.3.4.4 Hematology Laboratory Values of Interest Shift Tables

Table 14.3.4.5.1 Urinalysis Laboratory Summary (Continuous Results)

Table 14.3.4.5.2 Urinalysis Laboratory Summary (Categorical Results)

Table 14.3.4.5.3 Incidence and Severity of Application Site Burning – Shift Table

Table 14.3.4.5.4 Incidence and Severity of Application Site Itching – Shift Table

Table 14.3.4.5.5 Incidence and Severity of Application Site Dryness – Shift Table

Table 14.3.4.5.6 Incidence and Severity of Application Site Scaling – Shift Table

Table 14.3.4.5.7 Incidence and Severity of Application Site Erythema – Shift Table

Other Safety Data Summaries – Safety Population

Table 14.3.5.1 Summary of Vital Signs

Table 14.3.5.2 Summary of ECG parameters

Table 14.3.5.3 Incidence of Out of Range ECG parameters

Table 14.3.5.4 Summary of Status of ECGs (normal, abnormal not clinically significant, abnormal clinically significant)

Subject Data Listings – Safety Population

Discontinued Subjects

Listing 16.2.1.1.1 Subject Disposition (Completion or Discontinuation) & Compliance

Listing 16.2.1.1.2 Subject Disposition (visit dates)

Listing 16.2.1.2 Discontinued Subjects: Adverse Events

Protocol Deviations – Safety Population

Listing 16.2.2.1 Listing of Protocol Deviations

Listing 16.2.2.2 Eligibility: Inclusion/Exclusion Criteria

Subjects Excluded from the Efficacy Analysis

Listing 16.2.3.1 Listing of Subjects Excluded from the Efficacy Analysis

Demographic and Baseline Characteristics Data – Safety Population

Listing 16.2.4.1 Demographics and Baseline Characteristics

Listing 16.2.4.2 Medical History and Hyperhidrosis History

Listing 16.2.4.3 Prior and Concomitant Medications

Compliance and/or Drug Concentration Data – Safety Population

Listing 16.2.5.1 Investigational Product Accountability

Listing 16.2.5.2 Investigational Product Exposure

Individual Efficacy Response Data – Safety Population

Listing 16.2.6.1 Efficacy HDSM-Ax and HDSM-Ax, Child at Baseline and Change from Baseline

Listing 16.2.6.2 Efficacy PGI-S at Baseline and Change from Baseline

Adverse Event Listings (each Subject) – Safety Population

Listing 16.2.7.1 Adverse Event Listing

Listing 16.2.7.2 Serious Adverse Event Listing

Listing 16.2.7.3 Vital Signs

Listing 16.2.7.4 ECGs

Listing 16.2.7.5 ECG Abnormalities

Listing 16.2.7.6 Physical Examination

Listing 16.2.7.7 Application site burning, itching, dryness, scaling and erythema

Listing of Individual Laboratory Measurements by Subject - Safety Population

Listing 16.2.8.1 Clinical Chemistry Laboratory Measurements

Listing 16.2.8.2 Hematology Laboratory Measurements

Listing 16.2.8.3 Urinalysis Laboratory Measurements

Listing 16.2.8.3 Drug and Alcohol Screen

Listing 16.2.8.4 Pregnancy Testing

Other Data Listings – Safety Population, patients with respective comments

Listing 16.2.9.1 Case Report Form General Comments

Listing 16.2.9.2 Laboratory Data Comments

Listing 16.2.9.3 ECG Data Comments

15.2 Appendix B: Preliminary Table of Contents for Tables, Listings, Figures for PK

Tables

Table 14.x.x.1 Summary of Mean (SD), CV%, Median, Min and Max Sofpironium Plasma Concentrations (Ctrough values) by Week

Table 14.x.x.2 Summary of Mean (SD), CV%, Median, Min and Max Metabolite Plasma Concentration (Ctrough values) by Week

Listings

Listing 16.x.x.1 Individual Pharmacokinetic Sampling Times and Plasma Concentrations (Ctrough) values of Sofpironium by Week

Listing 16.x.x.2 Individual Pharmacokinetic Sampling Times and Plasma Concentrations (Ctrough) of Primary Metabolite by Week

Figures

Table of Content for Figures

Figure 14.x.x.1 Mean (±SD) Sofpironium Plasma Concentrations (Ctrough) versus Week (Linear Scale)

Figure 14.x.x.2 Mean (±SD) Primary Metabolite Plasma Concentrations (Ctrough) versus Week (Linear Scale)

Figure 14.x.x.3 Overlaid Individual Sofpironium Plasma Concentrations (Ctrough) versus Week (Linear Scale)

Figure 14.x.x.4 Overlaid Individual Primary Metabolite Plasma Concentrations (Ctrough) versus Week (Linear Scale)

15.3 Appendix C: 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.

---

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

15.4 Appendix D: 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.

---

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)

HDSM-Ax Version 1.3

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

15.5 Appendix E: 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