STATISTICAL ANALYSIS PLAN
10 August 2021 Amendment, Version 2.0

CONFIDENTIAL

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

PROTOCOL NUMBER: BBI-4000-CL-302

NCT03948646

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DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
0.1	08 October 2020	First Draft
0.2	27 October 2020	Add text regarding allergic contact dermatitis
1.0	29 October 2020	Clarification added to allergic contact dermatitis section, finalized for signature
1.1	06 July 2021	Changes: reference to protocol amendment in section 1 updated; demographics age category updated; duplicate subjects section 3.3 added; mITT population added for primary and key secondary end points, as well as sensitivity analyses for primary end points; convention for negative GSP values added; subgroup analyses added; AE text added about date imputation algorithm, local site reactions, figures, and overall summary table; formatting updates; update to TLF list; text added to Section 13; refined definition of confirmed ACD event and updated list of parameters to be summarized in Section 9.2.1.
2.0	10 August 2021	Changes: Section 8.3.7 update to PP analyses – PP is a completers population, so no multiple imputation is needed; Section 8.2.2 - analysis center pooling updated to add further combinations should models not converge; Sections 8.3.1 and 8.3.2 - method for combining p-values for site poolability added and method for selecting overall p-values for mixed effects model added; update to titles in TLF list

APPROVALS

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LIST OF ABBREVIATIONS

ACD	Allergic contact dermatitis
AE	Adverse event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
BBI-4000	Sofpironium bromide
CBI	Control Based Imputation
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CRF	Case report form
DLQI	Dermatology Life Quality Index
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of Treatment
GSP	Gravimetric sweat production
HDSM-Ax	Hyperhidrosis Disease Severity Measure-Axillary
ICH	International Council on Harmonisation
ITT	Intent-to-Treat
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measures
NMAR	Not Missing at Random
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PP	Per-protocol
REML	Restricted maximum likelihood
SAE	Serious adverse event
SD	Standard deviation
SI	Systeme International
TEAE	Treatment-emergent adverse event

WHO	World Health Organization

LIST OF IN-TEXT TABLES

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) contains detailed information to aid in the implementation of the statistical analyses and reporting of the study data for use in the clinical study report (CSR) for study BBI-4000-CL-302. This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data sets that will be used for analysis, as well as subject characteristics, efficacy, safety, and clinician-reported and patient-reported perception of disease severity and improvement parameters. The details of the specific statistical methods stated in the protocol will be provided and any changes from the protocol-specified analyses will be documented in the SAP prior to database lock. If additional analyses are required to supplement the planned analyses described in this SAP after the database lock, they may be completed and will be described in the CSR. Table, figure, and listing specifications are provided as an attachment in a separate document. This SAP amendment to version 1.1 dated July 06, 2021 is based on Amendment 3 of the BBI-4000-CL-302 protocol dated August 6, 2020 (Original September 27, 2019).

2. PROTOCOL SUMMARY

2.1 Study Objectives

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

Primary:

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

2.2 Study Endpoints

2.2.1 Primary Endpoints

There are 2 co-primary efficacy endpoints:

1. The proportion of subjects achieving at least a 2-point improvement in Hyperhidrosis Disease Severity Measurement-Axillary, 7-item (HDSM-Ax-7) scale score from baseline to end of treatment (EOT).
2. The change in gravimetric sweat production (GSP) from baseline to EOT.

2.2.2 Secondary Endpoints

The following secondary efficacy endpoints will be analyzed:

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

2.2.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints to be analyzed include the following:

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

- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-11 scale score and achieving at least a 70% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score and achieving at least a 50% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-11 scale score and achieving at least a 50% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- Change in HDSM-Ax-7 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57 as a continuous measure.
- Change in HDSM-Ax-11 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57 as a continuous measure.
- The proportion of subjects achieving at least a 70% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The proportion of subjects achieving at least a 50% reduction in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The rank-based GSP change from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The absolute GSP change from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The percent change from baseline in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The change in the Dermatology Life Quality Index (DLQI) (axilla) from baseline to Day 15 and Day 43 (EOT).

2.2.4 Safety Endpoints

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

2.3 Overall Study Design and Plan

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

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

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

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

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

2.4 Study Population

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

2.5 Treatment Regimens

Either sofpironium bromide gel, 15% or vehicle gel (placebo) topically applied to the axillae once daily at bedtime for 42 consecutive days.

2.6 Sample Size Determination

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

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

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

endpoints simultaneously is greater than 0.90 (with greater than 0.95 power for each of HDSM-Ax-7 and GSP). It is estimated that 350 total subjects will need to be randomized (in a 1:1 allocation) for there to be 300 subjects completing the co-primary efficacy assessments (approximately 15% drop-out rate).

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

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

3.1 Reporting Conventions

The following is a list of general analysis and reporting conventions to be applied to this study, unless otherwise specified.

All data displays (tables, listings, and figures) will have a header showing the sponsor company name, protocol number, page number, and display status (i.e. "DRAFT" or "FINAL"), as well as a footer indicating file name and run date/time. Summary tables and data listings will be summarized by treatment, as appropriate. All data collected per-protocol will be listed. Derived variables may also be listed.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)." If a count is 0, no percentage will be shown. If a percentage is 100%, 100% will be shown with no decimal place. To ensure completeness, summaries for categorical variables will include all categories, even if no subjects had a response in a particular category. Unless otherwise specified, the denominator for each percentage will be based on the number of subjects with available data in the population being summarized. If there are missing values, counts will be shown but will not be included in percentage calculations.

Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of subjects. The mean and median will be reported to an additional level of precision than the original observation in its rawest form (i.e. on the eCRF), and the SD and other measures of variability (e.g. standard error) will be reported to two additional levels of precision than the original observations. The minimum and maximum will be the same precision as the original data. In general, any calculated values, such as those due to unit conversion, will be rounded to the same number of decimal places as the original data.

Unless otherwise specified, all statistical tests will be 2-sided using α=0.05. Estimates and confidence intervals will be reported to 1 more decimal than the original data. P-values will be reported to 4 decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

Summary tables and data listings:

- No preliminary rounding will be performed; rounding will only occur after analysis.
- Data from subjects excluded from an analysis population will be presented in the data listings but will not be included in the calculation of summary statistics, where applicable.

- Data from each subject will be separated by a blank line. Within a data listing, if a descriptive item appears line after line (e.g., repetition of a subject number, date, visit, etc.), only the first occurrence will be displayed (e.g., in Listing of Vital Signs, subject number, date and visit will only be displayed on first row when presenting all parameters collected at same visit). Repetition of actual results or outcomes (e.g., Adverse Events (AEs), lab results, vital sign values, etc.) will not be collapsed.

- Data listings will be sorted by site, subject, treatment, and week and/or time of assessment, unless otherwise noted.

- When change from baseline is calculated, baseline is the last observation obtained prior to dosing of the study drug unless otherwise specified.

Mock tables and data listings will be provided as attachments to this analysis plan. Minor changes to the mocks after formal SAP approval will not necessitate re-approval unless changes to the text of the SAP are required.

All statistical deliverables will be produced, validated, and reviewed for accuracy/consistency in accordance with Rho, Inc. standard operating procedures and the processes described in the statistical validation plan.

SAS® (SAS Institute, Cary, North Carolina) statistical software, version 9.4 or later, will be used for all analyses. Adverse Events and Medical History will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization (WHO) Drug and Anatomical-Therapeutic-Chemical (ATC) classification and preferred term.

3.2 Standard Calculations

Unless otherwise noted, baseline is defined as the last observed data value prior to the receiving of the first application of treatment for treated subjects, and the last observed data value prior to the randomization date for randomized subjects who were not treated. The baseline derivation can include unscheduled visits.

Study day will be determined as:

- The assessment/event date minus the date of first dose of gel, if the assessment/event date is prior to the date of first dose of gel; and

- The assessment/event date minus the date of first dose of gel + 1, if the assessment/event date is on or after the date of first dose of gel. For example, Day 1 is defined as the date of the first dose of gel.

Note that if the subject is randomized but not treated then the randomization date will be Day 1 for Schedule of Event purposes. Change from baseline will be calculated as the post-baseline data value minus the baseline value. Percent change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "< 2.0") will be summarized as such in summary tables and figures. However, analysis will be performed using the numeric equivalent, e.g. "<2.0" will be analyzed as 2.0. Summary tables and figures will be footnoted when such practices occur.

Partial or missing dates used in calculations of duration may be imputed with logic similar to that of Adverse Events (Section 9.2).

3.3 Duplicate Subjects

During the course of the BBI-4000-CL-302 study, some subjects were identified as having registered for study participation at more than one site and/or in the first Phase 3 pivotal study (BBI-4000-CL-301); these subjects are said to be duplicate subjects. Duplicate subjects are identified as such in the individual study subject listings.

For analyses using the Intent-to-treat (ITT) Population or the Safety Population: (a) duplicate subjects with repeat registrations in the same study will have each registration analyzed as a different study subject with his/her unique subject ID; (b) For subjects who registered to both BBI-4000-CL-301 and BBI-4000-CL-302, the registrations will remain in each study as subjects for the respective study.

Duplicate subjects will be removed from the modified ITT (mITT) Population (See Section 4) for the co-primary efficacy endpoints, secondary efficacy endpoints and sensitivity analyses of the co-primary efficacy endpoints.

4. ANALYSIS POPULATIONS

Identification of the subjects to be included in each analysis population will be determined and finalized prior to database lock and unblinding. Subjects will be classified into the Safety, Intent-to-Treat (ITT), Per-Protocol (PP), and modified Intent-to-Treat (mITT) populations according to the following definitions:

Safety Population

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

Intent-to-Treat (ITT) Population

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

Per-Protocol (PP) Population

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

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

Modified Intent-to-Treat (mITT) Population

The mITT Population will be a subset of the ITT Population and excludes subjects with duplicate enrollments either within BBI-4000-CL-302 or across BBI-4000-CL-301 and BBI-4000-CL-302 (see Section 3.3). All other subjects will be analyzed according to the treatment group to which they were randomized, regardless of post-randomization protocol deviations, including no treatment or wrong treatment received.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Subject disposition will be summarized by treatment group for Safety, ITT, mITT, and PP populations separately. Summaries will include the number and percentage of subjects completing treatment, completing the study, and discontinuing the study early by the primary reason for discontinuation. The number and percentage of subjects excluded and reason for exclusion will be included in the PP population disposition table.

All subject disposition data will be listed by clinical site.

5.2 Protocol Violations

Major protocol violations will be summarized by treatment group for the Safety Population. Major protocol violations may include, but will not be limited to the following:

- Not meeting eligibility criteria;
- Randomization error;
- Received no protocol treatment or wrong treatment;
- Non-compliance with study drug dosing;
- On-study administration of a prohibited medication;
- Unauthorized changes to protocol procedure that could potentially affect subject safety or are a flagrant deviation of protocol defined procedures.

All major protocol violations will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the treatment group assignments. The number and percentage of subjects with any major protocol violations as well as the number and percentage of subjects with violations within each category will presented. A per subject listing will be provided for all protocol violations, major or minor, for the Safety Population.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic variables including age, sex, ethnicity, race, and predominant race, will be summarized by treatment group for the Safety, ITT, mITT, and PP Populations.

Age will be summarized using descriptive statistics. Age will also be categorized into 9-12, 13-16, 17-30, and ≥ 31 years of age. Age groups, sex, ethnicity, race, and predominant race will be summarized with the number and percentage of subjects in each parameter category. If more than one race is reported, subjects will be counted in each relevant category.

Baseline characteristics include medical history, height, weight, time since onset of axillary hyperhidrosis symptoms, and body mass index (BMI). Medical history will be summarized for the Safety Population. Other baseline characteristics will be summarized for the Safety, ITT, mITT, and PP Populations by treatment group.

Height, weight, BMI, and time since onset of axillary hyperhidrosis symptoms at baseline will be summarized using descriptive statistics. BMI will be calculated as: weight (kg) / (height (cm) / 100)^2. If height is entered in inches, height is converted to cm by Height (cm) = 2.54 *Height (inches). If weight is entered in lbs, weight is converted to kg by Weight (kg) = Weight (lbs) / 2.2046. Time since onset of axillary hyperhidrosis symptoms will be reported in months and calculated by dividing the duration in days by (365.25 / 12). Duration in days will be calculated as (date of informed consent – start date of axillary hyperhidrosis symptoms + 1).

Medical history events will be coded to system organ class using the most current version of MedDRA. Frequency counts and percentages will be used to summarize subjects reporting abnormal medical history by system organ class. Subjects reporting more than one event for a given system organ class will be counted only once for that system organ class. All demography, baseline characteristics, and medical history data collected will be presented in listings.

7. MEASUREMENTS OF STUDY TREATMENT EXPOSURE

Extent of study treatment exposure will be summarized for the Safety Population by treatment group. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one.

Study treatment exposure will be calculated for each subject by taking into account whether a subject took all doses of study drug as instructed through dosing deviations, including dose interruptions/modifications for AEs/tolerability, collected on the dosing page of the eCRF. For each dosing entry, study treatment exposure will be determined as the total number of doses received divided by the number of expected doses, multiplied by 100. As the standard dosing regimen is for study drug to be applied 1 time daily per axilla, the expected number of doses will be the number of days between the date of last dose of study drug minus the date of first dose of study drug, plus one, times two. The number of doses received will be the number of days between the date of last dose of study drug minus the date of first dose of study drug, plus one, multiplied by 2, minus the number of missed doses recorded on the dosing page of the eCRF.

Study treatment exposure will be calculated at the subject-level (i.e. across all dosing entries) and will be summarized using descriptive statistics.

Drug (pump) dispensation will be provided in a listing, to include total drug delivered per subject. Each pump will be primed, then weighed, prior to dispensing pumps to subjects. Each pump will be weighed upon return. Total drug delivered will be calculated as the total weight of all pumps dispensed minus the total weight of all returned pumps.

8. EFFICACY EVALUATION

8.1 Efficacy Endpoints

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

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

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

8.1.1 Definitions

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

HDSM-Ax

The HDSM-Ax-7 scale will be defined as the mean of the items in section No. 1 and questions 2a. through 2e. of the HDSM-Ax (7 sub-items in total). This will apply to both the ≥ 12 years of age scale and the 9-11 year old scale. The mean will be derived by taking the sum of 7 item scores and dividing it by 7. Subjects must answer all of the 7 sub-items for the HDSM-Ax-7 score to be evaluable/non-missing.

The HDSM-Ax-11 scale will be defined as mean of the items in sections No. 1, 2, and 3 of the HDSM-Ax (11 sub-items in total). This will apply to both the ≥ 12 years of age scale and the 9-11 year old scale. The mean will be derived by taking the total score and dividing by the number of questions answered. Subjects must answer at least 6 of the 11 sub-items for the HDSM-Ax-11 score to be evaluable/non-missing.

Baseline and End of therapy HDSM-Ax values are defined as follows:

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

GSP (both axillae combined total)

Baseline and End of therapy values are defined as follows:

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

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

DLQI (axilla)

The DLQI total score is calculated by summing answers to questions 1 through 10, including both parts of Question 7. The answer to each individual question is scored as follows'.

"Very much" = 3
"A lot" = 2
"A little" = 1
"Not at all" = 0
"Not relevant" = 0
Question 7, "prevented work or studying" = 3

All questions must be answered at the first DLQI assessment. Subsequent DLQI assessments missing an answer for a single question will be scored 0 for that question and totaled. Question 7 will be considered answered if Part 2 is answered even if No is not checked for Part 1. Subjects missing data for more than one question will have the instrument dropped for that visit.

Baseline and End of therapy values are defined as follows.

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

Patient Global Impression Scales; Severity (PGI-S) and Change (PGI-C)

PGI-S will be defined as Question #6 of the HDSM-Ax at each assessment. PGI-C will be defined as Question #7 of the HDSM-Ax at the Day 43 visit only.

8.1.2 Co-Primary Efficacy Endpoints

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

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

Note that the analysis of the HDSM-Ax co-primary efficacy endpoint will be conducted using 7 of the 11 items on the HDSM-Ax scale. More specifically, the mean of the 2 items in section 1 and the first 5 items in section 2 (7 sub-items in total) will be used. The mean will be derived by taking the sum of 7 item scores and dividing it by 7. For each of the HDSM-Ax sub-items, missing values at EOT will be imputed per Section 8.2.1.1 and Appendix 18.2. HDSM-Ax-7 at EOT will be derived from the imputed values.

8.1.3 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed:

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

8.1.4 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints to be analyzed include the following:

- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax-7 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 1-point improvement in the HDSM-Ax 11-Item (HDSM-Ax-11) scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.
- The proportion of subjects achieving at least a 2-point improvement in the HDSM-Ax-11 scale score from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43 (EOT), and 57.

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

- The rank-based GSP change from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The absolute GSP change from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The percent change from baseline in GSP from baseline to Days 8, 15, 22, 29, 36, 41, 42, 43, EOT, and Day 57.
- The change in the DLQI (axilla) from baseline to Day 15 and Day 43 (EOT).

8.2 Overview of Efficacy Analysis Issues

8.2.1 Handling of Dropouts or Missing Data

8.2.1.1 Multiple Imputations for Missing Data on Co-Primary Endpoints

For both HDSM-Ax-7 (diagram in Appendix 18.2) and GSP (diagram in Appendix 18.3), multiple imputations for missing EOT values in the vehicle group will be performed assuming Missing at Random (MAR). For the sofpironium bromide gel, 15% group, multiple imputations using a control-based imputations (CBI) model will be employed as the primary imputation method to handle missing EOT data. This approach will adopt a missing not at random (MNAR) assumption. It assumes that, due to discontinuing treatment, a subject who has been benefiting from sofpironium bromide gel, 15%, would maintain its benefit up to the last known efficacy endpoint value and from then on behave like a subject on vehicle. That is, the subject's efficacy trajectory after dropping out would be similar to that of a subject on vehicle with like subject characteristics and endpoint history up to the last observed visit for the sofpironium bromide gel, 15%, subject.

Twenty imputed datasets will be generated for each of the co-primary efficacy endpoints. The same co-primary analysis models (Section 8.3) will be applied to the multiple imputed datasets and the results combined via Rubin's rules (Rubin, 1976).

HDSM-Ax individual missing items scores will be imputed. If the individual item score is missing at Visit 12, but non-missing at either Visits 10 and or/ 11, then the closest (in time) non-missing score will be carried forward. If the individual item score is missing at all three visits of Visits 10, 11, and 12, then individual item scores will be imputed for all three visits. The mean will be derived from the imputed values. Further details are provided in Section 8.3.1 below.

GSP at EOT will only be multiply imputed if both the right and left axilla weights are missing at all three visits of Visits 10, 11, and 12. Further details are provided in Section 8.3.2 below.

8.2.1.2 GSP Data Outlier

The GSP assessment is known to be a highly variable measure. As such, two approaches will be applied to reduce the influence of large variations:

1) Prior to performing missing data imputations, if Normality of the GSP change from baseline to EOT data is violated by the Shapiro-Wilk test for either the vehicle arm or the sofpironium bromide gel, 15% arm, the GSP data will be rank-transformed at baseline and EOT and the difference in ranks will be used as the dependent variable in the primary efficacy model (Section 8.3.2)
2) Outlying GSP values will be removed from the imputation sampling database for missing data imputation purposes, as described below

In order to ensure that the missing data imputation method proposed is robust to outliers for the GSP co-primary endpoint, data from subjects that meet the criterion for being an outlier will be removed from the imputation sampling database as follows. Combining the vehicle and sofpironium bromide gel, 15% arms, the mean and standard deviation will be calculated for the non-missing GSP change from baseline to EOT data, i.e. the GSP primary outcome measure. Data values more than 3 standard deviations away from the mean will be regarded as outliers. However, since the outliers are included in the original mean and standard deviation calculations and would have inflated their values, the outliers will be set aside and the mean and standard deviation will be re-calculated to see if any additional outliers are identified. This process will be repeated until no more outliers are identified. Prior to performing imputation for missing GSP change from baseline data in the ITT population (Section 8.2.1.1) data values contributing to the outlying observations will be removed from the imputation sampling database, i.e. the non-missing vehicle data. With this approach, outlying data will not be propagated during missing data imputation. Once an imputation is complete, all original non-missing data (including outliers) and the imputed, previously missing, data will be used for the GSP ITT analysis.

8.2.1.3 Missing Data for all other Efficacy Endpoints

Unless otherwise specified, missing GSP and HDSM-Ax EOT data will be imputed for all ITT efficacy analyses.

8.2.2 Multicenter Studies

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

Should convergence issues occur due to small cell size for the covariate corresponding to analysis center, the following approach will be followed: a) analysis center will first be re-defined, continuing to group the largest and smallest centers together until there are at least 35 subjects per center; b) If convergence issues still occur after step a) has been completed then analysis center will be re-defined again, continuing to group the largest and smallest centers together until there are at least 70 subjects per center; c) if convergence issues still remain after implementing steps a) and b), the term for analysis center will dropped from the MI algorithm/statistical model.

If the convergence issue occurs in the generation of a MI dataset, all outcomes based on that dataset will use the same analysis center definition. All sensitivity analysis datasets will use the same analysis center definition and the models based off of those datasets will use that analysis center definition.

If the convergence issue occurs in modeling of an outcome, all models for that particular outcome will use the same analysis center definition. For example, if the grouping of at least 70 subjects per analysis center is required for the EOT analysis of ≥2-point improvement in HDSM-Ax-7, then all models at all time points of the ≥2-point improvement in HDSM-Ax-7 will use that analysis center definition. However, this would not impact the choice of analysis center for ≥1-point improvement in HDSM-Ax-7, nor the ≥2-point improvement in HDSM-Ax-11.

8.2.3 Assessment Time Windows

Allowable windows for each study visit are laid out in the Schedule of Events in Section 18.1. Assessments that occur outside of the allowable window for each study visit will be flagged as protocol deviations, but will be used in all analyses. In general, all data will be associated with the nominal study visit for which it was collected. Repeat assessments and unscheduled visits will be included in study listings, but will not be used in place of nominal timepoint data. It is not expected that there will be multiple measurements that occur within the same assessment time window. Should that occur, the closest measurement will be used in the analysis; an earlier measure will be used in case of a tie.

8.2.4 Multiple Comparisons/Multiplicity

A gated, fixed-sequence testing procedure will be used in this protocol to control the overall familywise false positive error rate for the primary and secondary endpoints analyses. The primary analysis will be regarded as positive and the trial will be successful for the co-primary efficacy endpoints if both null hypotheses are rejected in favor of sofpironium bromide gel, 15% at the 2-sided alpha = 0.05 level of significance (see hypotheses defined in Sections 8.3.1 and 8.3.2).

The three secondary efficacy endpoints are described in Section 8.1.3. If both co-primary analyses yield statistically significant results in favor of the sofpironium bromide gel,

15%, group, the three secondary efficacy endpoints will be tested in a fixed sequence in the order presented in Section 8.1.3. Testing will continue only if all previously tested null hypotheses have been rejected at the 2-sided alpha = 0.05 significance level in favor of sofpironium bromide gel, 15%.

8.2.5 Electronic Clinical Assessment Data

Gravimetric measurements of sweat production (GSP) and patient-reported outcomes HDSM-Ax, PGI-S, PGI-C, and Dermatology Life Quality Index (DLQI) (via electronic clinical outcomes assessment [eCOA] technology) will be recorded during the study at predefined timepoints. In the event that the eCOA data is not able to be captured via a device, the assessments will be recorded manually and the data entered into EDC. It is not expected that a subject will record both an electronic and a manual assessment for an outcome at any given timepoint. However, if duplicate data do exist, then the eCOA value will be used in the analysis.

8.3 Analysis Methods

With the exclusion of Section 8.3.7 Exploratory Efficacy Analyses, all other Section 8.3 analyses will be repeated for the mITT population.

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

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

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

8.3.1 Primary Analysis of the HDSM-Ax-7 Co-Primary Endpoint

The primary analysis of the HDSM-Ax-7 co-primary endpoint will use the 2-point responder status at EOT. If a subject is missing any of items 1a, 1b, 2a, 2b, 2c, 2d, or 2e Visit 4 (Day 1) value, Visit 1 (Screening) value will be used as Baseline. If Visit 1 (Screening) value is also missing, subject will be excluded from all HDSM-Ax-7 change from baseline analyses. If a subject is missing Day 43 value, the closest (in time) available non-missing value from Day 41 (±2 days) or Day 42 (±2 days) will be used as the first level of imputation. Should none of the Days 41, 42, and 43 values be available, multiple imputations of missing EOT (i.e. Day 43) item-level scores will be performed on the sofpironium bromide gel, 15% arm values using CBI methodology (Section 8.2.1.1 and Appendix 18.2). Multiple imputations assuming MAR will be performed for missing data for Vehicle subjects. The HDSM-Ax-7 score will be calculated using the imputed

item-level values. No other missing value imputation will be performed in this co-primary analysis.

The analysis will use a logistic regression model.

The following covariates are planned:

- Treatment (class effect: sofpironium bromide gel, 15% group, vehicle)
- Baseline HDSM-Ax-7 total score
- Analysis center (see Section 8.2.2)

The null hypothesis to be tested for the primary analysis of the HDSM-Ax-7 co-primary endpoint is as below:

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

$$H_0: P_A = P_P ;$$

where P_A and P_P represent the true underlying proportion of subjects achieving at least a 2-point improvement in HDSM-Ax-7 for Treatment A (sofpironium bromide gel, 15%) and Treatment P (vehicle), respectively.

The null hypothesis will be tested against the two-sided alternative hypothesis as below:

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

$$H_1: P_A \neq P_P ;$$

Within the model specified above, a comparison will be made of the proportion of ≥2-point HDSM-Ax-7 responders at EOT in the sofpironium bromide gel, 15%, and vehicle groups. The estimand of this co-primary efficacy analysis is the difference in proportions between sofpironium bromide gel, 15%, and vehicle with a ≥2-point improvement from baseline to EOT in HDSM-Ax-7 total scores among all ITT subjects, regardless of treatment adherence. The comparison will be conducted using a two-sided test at an alpha = 0.05.

A separate, site poolability analysis will be performed with analysis center-by-treatment interaction terms added to the primary analysis model. The overall p-value for the analysis center-by-treatment interaction terms will be determined by averaging the Chi-squared test statistics across the 20 imputations, then calculating the p-value based on that average. An overall $p < 0.10$ for the combined interaction terms will be regarded as an indication of potential heterogeneity among the analysis centers. A mixed effects logistic regression model analysis will then be performed with analysis center as a random effect to account for the potential heterogeneity. The overall p-value for the analysis center

random effect will be derived from the covariance parameter estimates across the 20 imputations.

8.3.2 Primary Analysis of the GSP Co-Primary Endpoint

The primary analysis of the GSP co-primary endpoint will use all available GSP change from baseline scores at EOT. Missing baseline continuous GSP data (i.e. missing data for all Visits of 2, 3, 4) will be imputed using the Screening GSP data. If Screening GSP data is also missing, subject will be excluded from all GSP change from baseline analyses.

For GSP change from baseline to EOT data, univariate checks will be performed prior to performing multiple imputations for missing data. The Shapiro-Wilk test will be applied to assess Normality of the model residuals separately for sofpironium bromide gel, 15% arm, and vehicle arm. Should the assumption of Normality not be violated for both treatment arms, then GSP change from baseline to EOT values will be analyzed as continuous data. The median of continuous GSP data from Visits 2, 3, and 4 will be used as the baseline value for a subject, and the median of continuous GSP data from Visits 10, 11, and 12 will be used as the EOT value. For each subject, the difference between the baseline and EOT GSP values (EOT – baseline) will serve as the outcome value for the GSP ANCOVA analysis.

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

Missing EOT GSP data (continuous data), for each of Days 41, 42, and 43 will be imputed before analysis is performed for subjects missing both axillae at all 3 visits. If at least one axillae is non-missing at Day 41, 42, or 43, then the EOT value will be considered non-missing. For continuous data, subjects with results (Section 8.2.1.2) meeting the criterion for "outlier" will be removed from imputation sampling database (i.e., data for vehicle subjects) prior to missing data imputation. From the appropriate imputation sampling database, multiple imputations of missing EOT sofpironium bromide gel, 15% arm GSP values will be performed using a CBI methodology (Section 8.2.1.1 and Appendix 18.3). Multiple imputations assuming MAR will be performed for missing EOT data Vehicle subjects.

The model specified is an ANCOVA model (either non-ranked or ranked).

The following fixed effects are planned:

- Treatment (class effect: sofpironium bromide gel, 15% group, vehicle)
- Baseline GSP (either non-ranked or ranked)
- Analysis center (see Section 8.2.2)

The null hypothesis to be tested for the primary analysis of the GSP Co-primary endpoint is as below:

H_0: The GSP changes (or rank-based changes) from baseline to EOT are the same in the sofpironium bromide gel, 15%, and vehicle groups, i.e.

$$H_0: \mu_A = \mu_P;$$

where μ_A and μ_P represent the true mean change (or rank-based change) in GSP scores for Treatment A (sofpironium bromide gel, 15%) and Treatment P (vehicle), respectively.

The null hypothesis will be tested against the two-sided alternative hypothesis as below:

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

$$H_1: \mu_A \neq \mu_P;$$

The ANCOVA model used in this analysis will be the same, regardless of whether continuous or rank-based GSP data is used. Within the model specified above, a comparison will be made (using LS mean contrasts) to compare the change (or rank-based change) from baseline to EOT for GSP in the sofpironium bromide gel, 15%, and vehicle groups. The estimand of this co-primary efficacy analysis is the mean treatment difference, sofpironium bromide gel, 15%, versus vehicle, in change from baseline (or rank-based change from baseline) to EOT for GSP among all ITT subjects, regardless of treatment adherence. The comparison will be conducted using a two-sided test at an alpha = 0.05.

For the primary endpoint of either ranked or continuous GSP (pending normality test results), a separate, site poolability analysis will be performed with analysis center-by-treatment interaction terms added to the primary analysis model. The overall p-value for the analysis center-by-treatment interaction terms will be determined by averaging the F test statistics across the 20 imputations, then calculating the p-value based on that average. An overall $p < 0.10$ for the combined interaction terms will be regarded as an indication of potential heterogeneity among the analysis centers. A mixed effect ANCOVA model analysis will then be performed with analysis center as a random effect to account for the potential heterogeneity. The overall p-value for the analysis center random effect will be derived from the covariance parameter estimates across the 20 imputations.

8.3.3 Supportive Analysis of the HDSM-Ax-7 Co-Primary Endpoint

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

8.3.4 Supportive Analysis of the GSP Co-Primary Endpoint

Two supportive analyses will be performed for the GSP co-primary endpoint:

(1) If the Shapiro-Wilk test for Normality of the GSP baseline to EOT data is violated, then, using the same methodology as described in Section 8.3.2, an ANCOVA analysis will be performed for the non-rank-transformed, continuous GSP data. The model will use the fixed effects of treatment, baseline GSP, and analysis center. If the Shapiro-Wilk test for Normality of the GSP baseline to EOT data is not violated and the continuous GSP is used for the co-primary endpoint, then the ranked GSP ANCOVA analysis will be performed as a supportive analysis.

(2) To further address the potential large variations in GSP data, mixed model repeated measures (MMRM) analyses will be performed to estimate the average sofpironium bromide gel, 15% treatment effect over the 6 week course of treatment, i.e. the average sofpironium bromide gel, 15% versus vehicle difference from baseline to Days 8, 15, 22, 29, 36, and EOT, using both rank-based and non-rank-based data. As the MMRM methodology is known to be robust to missing data, missing data will not be imputed for this analysis.

The model specified is a REML-based analysis with an identity link.

The following fixed effects are planned:

- Treatment (class effect: sofpironium bromide gel, 15% group, vehicle)
- Visit (visits will be coded as ordinal, where Visit 5 = 1, Visit 6 =2, Visit 7 = 3, Visit 8 = 4, Visit 9 = 5, EOT = 6)
- Baseline GSP (ranked or non-ranked, depending on the model)
- Analysis center
- Baseline-by-visit interactions
- Treatment-by-visit interactions

Based on the Study BBI-4000 CL-203 results, significant treatment versus visit interactions are not expected. Nevertheless, should treatment versus visit interactions be significant (i.e. $p<0.05$), the estimated treatment effect at EOT will be reported. An unstructured correlation matrix will be used to model the variance and covariance of within-subject repeated measures and restricted maximum likelihood estimation. The

Kenward-Roger method will be used for the denominator degrees of freedom. In order to arrive at the correct structure for the data, if the model fails to converge using an unstructured covariance matrix, other covariance structures will be tested as follows: heterogeneous Toeplitz (TOEPH), heterogeneous AR(1) (ARH1), heterogeneous compound symmetry (CSH), Toeplitz (TOEP), spatial power with numeric visit number SP(POW)(VISn), autoregressive (1) (AR(1)), and compound symmetry (CS). The model that converges with the lowest Akaike Information Criterion (AIC) will be used. If the treatment-by-visit interactions are not significant overall, they will be removed from the final model; similarly for the baseline-by-visit interactions.

8.3.5 Sensitivity Analyses of the Co-Primary Efficacy Endpoints

As stated in Section 8.2.1.1, multiple imputations procedures for missing HDSM-Ax-7 and GSP values will be performed prior to the co-primary efficacy analyses under MAR and MNAR assumptions. In order to support the results of the co-primary GSP analysis, the ranked GSP and non-rank-transformed GSP ANCOVA analyses will be repeated without imputing missing data, and again after removing outlier data. To further explore the robustness of the primary analysis results to different missing data assumptions, analyses using two additional imputation methods will be performed as presented below. The first is an analysis of the HDSM-AX-7 co-primary endpoint with missing data imputed as failure/non-response. The second is a tipping point analysis on both co-primary endpoints, using multiple imputations for missing data. Additionally, the 7 items in the HDSM-Ax-7 scale will be analyzed individually to support the primary analysis for this co-primary endpoint. The below sensitivity analyses will be performed using the ITT Population and the mITT Population.

Table 8-2 Summary of Sensitivity Analyses of the Co-Primary Efficacy Endpoints

Sensitivity Analysis Number	Co-Primary Efficacy Outcome Assessed	Sensitivity Analysis	Populations
1	GSP change from baseline to EOT	Analysis performed on available data only without imputing missing data; using both ranked and non-ranked data.	ITT, mITT

2	GSP change from baseline to EOT	Subjects with outlying data removed from analysis; using both ranked and non-ranked data (multiple imputations for missing data).	ITT, mITT
3	HDSM-Ax-7 2-point improvement from baseline to EOT	Missing data imputed as failure/non-response (single imputation only)	ITT, mITT
4	HDSM-Ax-7 2-point improvement and GSP change from baseline to EOT	Tipping point analysis (multiple imputations for missing data)	ITT, mITT
5	HDSM-Ax-7 2-point improvement from baseline to EOT	Analysis of the influence of the 7 individual items in the HDSM-Ax-7 scale (multiple imputations for missing data)	ITT, mITT

8.3.5.1 Sensitivity Analysis 1: GSP, All Available Data, no Imputations

To further investigate the robustness of the GSP co-primary efficacy endpoint, the ranked and non-rank-transformed GSP analyses will be repeated on all available data only without imputing missing data. The exact same analysis models (ANCOVA) will be used on the observed ranked and non-ranked change in GSP from baseline to EOT.

8.3.5.2 Sensitivity Analysis 2: GSP, Outlying Data Removed, Multiple Imputations

To further investigate the robustness of the GSP co-primary efficacy outcome, the ranked and non-rank-transformed GSP analyses will be repeated with outlier data (as defined in

Section 8.2.1.2) removed from the analysis data set (both sofpironium bromide gel, 15% group and vehicle group) before any endpoint analysis is performed. The methodology will be similar to the primary analysis of the GSP co-primary endpoint. For missing data imputation purposes, outlier data will also be removed from the imputation sampling database. The exact same analysis models (ANCOVA) will be used on the observed ranked and non-ranked change in GSP from baseline to EOT. This differs from the analysis of the GSP co-primary endpoint, in that outlier GSP data is kept in the primary analysis but removed for this sensitivity analysis.

8.3.5.3 Sensitivity Analysis 3: HDSM-Ax-7, Missing Data imputed to Failure/Non-Response

In this analysis, missing EOT HDSM-Ax-7 cases will be analyzed as failure/non-responder in both treatment groups. The same co-primary HDSM-Ax-7 logistic regression model will be re-run on the HDSM-Ax dataset subjects with missing data modelled as not having improved by at least 2 points. The treatment success proportions estimates will also be reported.

8.3.5.4 Sensitivity Analysis 4: HDSM-Ax-7 and GSP, Tipping Point Analysis

A tipping point analysis will be conducted to investigate what type of missing data would cause a positive between-arm comparison of the outcomes of the co-primary efficacy endpoints to be non-significant. These analyses will be conducted separately for the HDSM-Ax-7 and GSP co-primary endpoints.

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

For the HDSM-Ax-7 co-primary endpoint, identical imputation methodology to that described above for the GSP will be applied to the HDSM-Ax-7 total scores, and the resulting values will be dichotomized into responders using the 2-point improvement criteria. A Δ increment of 0.5 (in a 0-4 scale) will be used for this study. The HDSM-Ax-7 co-primary efficacy outcome analysis methodology will be applied to the imputed datasets and repeated until statistical significance no longer holds. The tipping point at which the results are no longer significant will be identified and the results will be summarized graphically.

8.3.5.5 Sensitivity Analysis 5: Analysis of the Influence of 7 individual items in the HDSM-Ax-7 scale

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

8.3.6 Secondary Efficacy Analyses

The three secondary efficacy endpoints are described in Section 8.1.3.

If both co-primary analyses yield statistically significant results in favor of the sofpironium bromide gel, 15% group, the three secondary efficacy endpoints will be tested in the ITT population in a fixed sequence in the order presented in Section 8.1.3. Testing will continue only if all previously tested null hypotheses have been rejected at the 2-sided alpha < 0.05 significance level in favor of sofpironium bromide gel, 15%.

The analysis of the three responder secondary endpoints specified in Section 8.1.3 will be conducted using the same logistic regression model as that used for the HDSM-Ax-7 co-primary efficacy analysis. For each model, the covariates include treatment, baseline parameter score, and analysis center. For the composite endpoints, both HDSM-Ax-7 baseline and GSP baseline will be included as covariates.

8.3.7 Exploratory Efficacy Analyses

The exploratory efficacy endpoints are fully described in Section 8.1.4. All exploratory efficacy endpoints that involve a proportion of responders will be analyzed using methods similar to what was described for the HDSM-Ax-7 co-primary endpoint. For each endpoint, a logistic regression model will be generated using planned covariates of treatment, baseline parameter, and analysis center. For the composite endpoints, both baseline HDSM-Ax and GSP will be included as covariates.

All other exploratory endpoints that involve a change from baseline to a single timepoint for a continuous variable will be analyzed using methods similar to what is described for the GSP co-primary endpoint. For each endpoint, an ANCOVA model will be generated with fixed effects for treatment, baseline parameter, and analysis center.

Change in PGI-S from baseline and PGI-C score (only collected at Day 43) will be analyzed using a Cochran-Mantel Haenszel (CMH) test for ordinal data to compare the treatment arms at each visit.

All exploratory efficacy analyses will be based on available data and missing GSP and HDSM-Ax EOT data imputed per Section 8.2.1. HDSM-Ax-11 will be calculated in the same manner as HDSM-Ax-7 at EOT, where the mean is derived from imputed sub-items for the EOT score. In addition, all continuous parameters will be summarized by visit on the ITT population.

Data in the analysis of rank-based GSP change from baseline to each timepoint will be ranked in the same manner as that of the co-primary GSP endpoints (Section 8.3.2).

Proportion of subjects achieving 1- and 2-point improvement from baseline in HDSM-Ax-7 and HDSM-Ax-11 will be plotted at each timepoint. Similar plots will be generated for proportion of subjects achieving 50% and 70% reduction in GSP from baseline at each timepoint and for the secondary composite endpoints. Plots will be generated for change from baseline for continuous measures over time.

In addition, a summary table of frequency of missing measurements at each visit will be generated for GSP and HDSM-Ax-7, separately.

All secondary and exploratory efficacy endpoints will be analyzed for both the ITT and PP populations. The co-primary endpoint primary analyses will also be analyzed for the PP population as an exploratory analysis. Analyses completed on the PP population will not be multiply imputed. The PP population is a completers population and analyses based on this population will use observed data. P-values for exploratory efficacy endpoints will be provided for descriptive purposes only and no formal hypothesis testing will occur.

8.4 Examination of Subgroups

While the study is not powered to show efficacy for pre-defined subgroups, the co-primary efficacy end points will be further analyzed by subgroups of interest . All p-values from the subgroup tables will be of an exploratory nature, as no formal hypothesis testing will occur.

The primary analyses for the primary endpoints (see sections 8.3.1 and 8.3.2) will be repeated for the ITT population for the following subgroups:

- Age group: < 17 years, ≥17 to 30 years, ≥31 years.
- Gender: male, female.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino or not reported.
- Race: white, non-white or not reported.

Race and ethnicity categories have been combined due to potential small sample size. For age group, should the models fail to converge due to small cell size, age categories may

be further collapsed. For all subgroup models, should the models fail to converge, NA or not assessable or similar will be displayed.

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

Safety analyses will be carried out for the Safety Population. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analyses. Allowable windows for each study visit are laid out in the Schedule of Events in Section 18.1. Assessments that occur outside of the allowable window for each study visit will be flagged as protocol deviations, but will be used in all safety analyses. In general, all data will be associated with the nominal study visit for which it was collected. Repeat assessments and unscheduled visits will be included in study listings, but will not be used in place of nominal timepoint data. It is not expected that there will be multiple measurements that occur within the same assessment time window. Should that occur, the closest measurement will be used in the analysis; an earlier measure will be used in case of a tie. No formal hypothesis testing will be performed.

9.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those adverse events (AEs) with onset during or after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by treatment group and severity.

Partial or completely missing AE start dates will be imputed as follows:

1. If the year and month are known:
    a. If the year and month are the same as the year and month of the treatment start date, impute to treatment start date.
    b. Otherwise, use the 1st of the month.
2. If only the year is known:
    a. If the year is the same as the year of treatment start date, impute to treatment start date.
    b. Otherwise, impute to January 1st of that year.
3. If the date is completely missing, impute to treatment start date.

Partial or completely missing AE end dates will be imputed in the same manner, with end of treatment date or end of study replacing treatment start date in the algorithm.

AE listings will display the imputed dates.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the latest version of MedDRA.

At Visits 5, 6, 7, 8, 9, 12 (EOT), and 13 (Follow-up), treatment-emergent adverse events (TEAEs) in the Safety Population will be summarized by severity in the following tables: all reported TEAEs, all SAEs, all treatment-related SAEs, treatment-related TEAEs, severe TEAEs, TEAEs leading to dose interruption, TEAEs leading to study discontinuation, TEAEs of special interest, and anticholinergic TEAEs. Additionally, local site reaction TEAEs will be summarized in the Safety Population by severity at Visits 5, 6, 7, 8, 9, 12 (EOT), and Visit 13 (Follow-up). Local site reaction TEAEs are defined as AEs coded to the system organ class of general disorders and administration site conditions and, at a minimum, the following preferred terms:

- Application site pruritus
- Application site pain
- Application site irritation
- Application site dermatitis
- Application site rash
- Application site erythema
- Application site discolouration
- Application site dryness
- Application site exfoliation
- Application site reaction
- Application site warmth

Each of the above tables will be produced for cumulative TEAEs up to the current visit reported by all Safety Population subjects (including those absent from the current visit). At each of the visits, each of the above tables will summarize the subject incidence (frequency count and %) for the specified TEAE, mapped to MedDRA System Organ Class and Preferred Term, according to the highest severity reported. Subjects with only unknown severity for a TEAE will be counted under the severity unknown category.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class in the total column and preferred term within each system organ class. The total column will not be displayed and will only be used for sorting. TEAEs of special interest include the following:

- Vision blurred
- Mydriasis (unilateral or bilateral)
- Urinary hesitation

An overall TEAE summary table by treatment group with the total number of TEAEs and the number and percentage of subjects with at least one of the following will be presented: TEAE, serious TEAE, treatment-related TEAE, treatment-related serious TEAE, severe TEAE, TEAE leading to dose interruption, TEAE leading to study discontinuation, TEAEs of special interest, anticholinergic TEAEs, anticholinergic TEAEs leading to study discontinuation, local site reaction TEAEs, local site reaction TEAEs leading to study discontinuation. The overall summary table will also display the number and percent of subject deaths, should any deaths occur.

The number of subjects with study discontinuations due to TEAEs, the number of subjects with study discontinuations due to anticholinergic TEAEs, and the number of subjects with study discontinuations due to AESIs will be plotted as a bar chart versus time on treatment. Time on treatment is defined as the earlier of treatment end date or study discontinuation date – treatment start date + 1. Time on treatment will be displayed in categories of 0 to 2 weeks, >2 to 4 weeks, >4 to 6 weeks. Weeks are defined as 7 days. The follow-up visit is excluded.

The number of treatment-related TEAEs and the number of local site reaction TEAEs will be plotted versus time on treatment. The number of subjects with a treatment-related TEAE and the number of subjects with a local site reaction TEAE will be plotted versus time. Time for these plots will be displayed as weeks 1-8 which includes the follow-up visit.

Adverse event data will be presented in data listings by subject, treatment group, and event. SAEs, TEAEs leading to study discontinuation, TEAEs of special interest, and anticholinergic TEAEs will be presented in separate data listings. Death is not expected. However, should death occur on study, the event will be reported with detailed narratives.

9.2.1 Allergic Contact Dermatitis

Allergic contact dermatitis (ACD), as an AE, may manifest as moderate to severe pruritus and moderate to severe erythema with or without vesicles or bullae.

In the case of a suspected AE of ACD, the Medical Monitor should be contacted to discuss the case and the following steps should be taken at the discretion of the Investigator: 1) assigned treatment should be withheld, 2) the AE of ACD documented, 3) any necessary concomitant treatment should be administered, which can include topical corticosteroids.

Once the AE of ACD is resolved in the opinion of the Investigator, any concomitant therapy for this AE should be stopped, and the assigned treatment should be restarted after discussion with the Medical Monitor (i.e., re-challenge exposure). If there is a recurrence, ACD is confirmed and should be documented as an AE that is related to the assigned study treatment.

Confirmed ACD cases are defined as cases which led to recurrence of ACD event following treatment restart. Suspected ACD cases are those events with “Suspected Allergic Contact Dermatitis” checked on the AE eCRF page.The following parameters will be summarized with descriptive statistics by treatment group to characterize instances of ACD:

- Number and percentage of subjects with treatment-emergent ACD events by severity
- Number and percentage of subjects with treatment-emergent ACD events leading to treatment discontinuation by severity

- Number and percentage of subjects who restarted treatment after the ACD event and later discontinued treatment. These will be confirmed ACD events.
- Time to first confirmed ACD event in days defined as: start date of the ACD event - treatment start date + 1.
- Time to first treatment interruption due to confirmed ACD event in days defined as: last exposure date prior to ACD event leading to interruption - treatment start date + 1.
- Duration of treatment interruption in days defined as: date of first exposure after end of ACD event - date of last exposure prior to ACD event leading to interruption + 1. If the ACD event is ongoing, either the treatment discontinuation date or first available exposure date after the start of the event will be used to calculate duration. If subject experienced more than one interruption due to ACD, durations of interruptions will be summed.
- Time to treatment discontinuation in days defined as: date of treatment discontinuation - date of treatment start + 1.
- Time from treatment restart to treatment discontinuation due to recurrence ACD event in days defined as: date of treatment discontinuation – date of first exposure after end of ACD event + 1.

Percentages will be out of the Safety Population in each group. A by-subject listing will also be presented.

9.3 Local Tolerability Assessments

Local tolerability assessments are performed for both axillae individually at visits 4, 5, 6, 7, 8, 9, 12 (EOT), and 13 (follow-up). Visit 4 data are the baseline. Should Visit 4 data be missing, baseline will be derived as the last value prior to first dose and as such unscheduled visits may be included. Subjects rate the severity of any symptoms of burning, stinging, or itching at the application-site on a scale of 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. Investigators assess the drug application site for the existence of significant local symptoms of scaling and erythema on a scale of 0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe. For any symptoms, subject severity is the worst severity of the two axillae.

Subject and Investigator assessments will be included in tables and listings. Tables will be presented by treatment arm. An overall summary table will be presented with subject incidences tabulated according to the worst severity experienced while on study. At each visit, local tolerability assessments will also be descriptively summarized by severity. Additionally, at each post-baseline visit, local tolerability will be summarized as cumulative shift tables vs. baseline. Subject counts for each symptom will be cross-tabulated with baseline severity according to the maximum post-baseline severity reported for either axilla up to the current visit. Local tolerability assessment results will also be plotted by severity, displaying counts for any symptom, burning, stinging, itching, scaling, and erythema. A symptom is counted if the severity scale is rated >0.

9.4 Clinical Laboratory Evaluation

Safety laboratory parameters (hematology, chemistry, urinalysis) will be collected at the Screening Visit and EOT Visit. Urine pregnancy results will be collected at visits 1, 4, 8, and 12 (EOT). Laboratory parameters will be presented in Systeme International (SI) units and descriptively summarized for values at each visit and for changes from baseline at each subsequent visit. Unscheduled visits and early termination visits will be included.

Laboratory parameters to be summarized and listed include hematology, clinical chemistry, and routine urinalysis. Urine pregnancy test results will be listed only.

9.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1 Vital Signs

Vital signs measurements will be collected at Visits 4, 5, 6, 7, 8, 9, 12 (EOT), and 13 (follow-up). Visit 4 data are the Baseline. Should Visit 4 data be missing, baseline will be derived as the last value prior to first dose (e.g. Screening), and, as such, unscheduled visits may be included. Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature. Vital sign parameters will be descriptively summarized for values at each visit and for changes from baseline at each subsequent visit. Vital signs will also be listed.

9.5.2 Physical Examinations

Physical examination results will be collected at Visit 4 only. Physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes, and extremities. Height and weight will also be measured and recorded. Results of the physical examination will be presented in subject data listings by subject, study visit, and body system.

9.5.3 Other Safety Measures

9.5.3.1 Prior and Concomitant Medications

Medications will be coded using the latest version of the World Health Organization (WHO) drug dictionary. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately and the study phase of each medication will be determined programmatically based on medication start and end dates. Partial or missing start and end dates will be imputed according to Section 9.2.

A prior medication is defined as any medication started prior to the date of the first dose of study drug. A concomitant medication is defined as any medication started on or after the date of the first dose of study drug.

For the summary of both prior medications and concomitant medications, the number and percentage of subjects receiving any medication will be summarized by treatment group, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant,) will be presented on the listing of prior and concomitant medications.

Prior or concomitant therapies and procedures will be listed only.

10. PHARMACOKINETIC/PHARMACODYNAMIC EVALUATION

Pharmacokinetic and pharmacodynamic analyses are not part of this study protocol.

11. OTHER ANALYSES

11.1 Psychometric Analysis of the HDSM-Ax-7

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

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

12. INTERIM ANALYSES AND DATA MONITORING

There are no interim analyses planned, nor is there a plan to establish a data monitoring committee for this study.

13. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Due to the issue of duplicate subjects discussed in Section 3.3, the mITT analysis population was added. Definition of local site reaction TEAEs and analysis of local site reaction TEAEs was added.

14. REFERENCES

1. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581–590.

15. LIST OF PLANNED TABLES

Number	Title	Population
14.1.1.1.1	Summary of Subject Disposition and Reasons for Discontinuation	Safety
14.1.1.1.2	Summary of Subject Disposition and Reasons for Discontinuation	Intent-to-treat
14.1.1.1.3	Summary of Subject Disposition and Reasons for Discontinuation	Per-protocol
14.1.1.1.4	Summary of Subject Disposition and Reasons for Discontinuation	Modified Intent-to-treat
14.1.1.2	Summary of Major Protocol Violations	Safety
14.1.2.1	Summary of Demographic Characteristics	Safety
14.1.2.2	Summary of Demographic Characteristics	Intent-to-treat
14.1.2.3	Summary of Demographic Characteristics	Per-protocol
14.1.2.4	Summary of Demographic Characteristics	Modified Intent-to-treat
14.1.3.1	Summary of Baseline Characteristics	Safety
14.1.3.2	Summary of Baseline Characteristics	Intent-to-treat
14.1.3.3	Summary of Baseline Characteristics	Per-protocol
14.1.3.4	Summary of Baseline Characteristics	Modified Intent-to-treat
14.1.4	Summary of Medical History	Safety
14.1.5	Summary of Prior Medications by Drug Class and Generic Drug Name	Safety
14.2.1.1.1	Co-Primary Analysis: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.1.2	Co-Primary Analysis: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Per-protocol
14.2.1.1.3	Co-Primary Analysis: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.1.4	Co-Primary Analysis: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.1.5	Co-Primary Analysis: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Multiple Imputations	Per-protocol

* Primary GSP endpoint is dependent on normality test results. If the normality is violated, the primary GSP endpoint will use ranked data. If the normality is not violated, the primary GSP endpoint will use continuous data.

Number	Title	Population
14.2.1.1.6	Co-Primary Analysis: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.1.7	Summary of Normality Test Results for GSP	Intent-to-treat
14.2.1.2.1	Supportive Analysis for HDSM-AX-7: ANCOVA Analysis of Change in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.2.2	Supportive Analysis for HDSM-AX-7: ANCOVA Analysis of Change in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.3.1	Supportive Analysis 1 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.3.2	Supportive Analysis 1 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.4.1	Supportive Analysis 2 for GSP: Mixed Model Repeated Measures Analysis of Change in Ranked GSP - No Imputation	Intent-to-treat
14.2.1.4.2	Supportive Analysis 2 for GSP: Mixed Model Repeated Measures Analysis of Change in Ranked GSP - No Imputation	Modified Intent-to-treat
14.2.1.5.1	Supportive Analysis 3 for GSP: Mixed Model Repeated Measures Analysis of Change in Continuous GSP - No Imputation	Intent-to-treat
14.2.1.5.2	Supportive Analysis 3 for GSP: Mixed Model Repeated Measures Analysis of Change in Continuous GSP - No Imputation	Modified Intent-to-treat
14.2.1.6.1	Sensitivity Analysis 1 for GSP: ANCOVA Analysis of Change in Ranked GSP from Baseline to End of Treatment - No Imputation	Intent-to-treat
14.2.1.6.2	Sensitivity Analysis 1 for GSP: ANCOVA Analysis of Change in Ranked GSP from Baseline to End of Treatment - No Imputation	Modified Intent-to-treat
14.2.1.7.1	Sensitivity Analysis 1 for GSP: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment - No Imputation	Intent-to-treat
14.2.1.7.2	Sensitivity Analysis 1 for GSP: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment - No Imputation	Modified Intent-to-treat

Number	Title	Population
14.2.1.8.1	Sensitivity Analysis 2 for GSP: ANCOVA Analysis of Change in Ranked GSP from Baseline to End of Treatment with Outliers Removed - Multiple Imputations	Intent-to-treat
14.2.1.8.2	Sensitivity Analysis 2 for GSP: ANCOVA Analysis of Change in Ranked GSP from Baseline to End of Treatment with Outliers Removed - Multiple Imputations	Modified Intent-to-treat
14.2.1.9.1	Sensitivity Analysis 2 for GSP: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment with Outliers Removed - Multiple Imputations	Intent-to-treat
14.2.1.9.2	Sensitivity Analysis 2 for GSP: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment with Outliers Removed - Multiple Imputations	Modified Intent-to-treat
14.2.1.10.1	Sensitivity Analysis 3 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-AX-7 from Baseline to End of Treatment - Non-responder Imputation	Intent-to-treat
14.2.1.10.2	Sensitivity Analysis 3 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-AX-7 from Baseline to End of Treatment - Non-responder Imputation	Modified Intent-to-treat
14.2.1.11.1	Sensitivity Analysis 4 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Tipping Point Analysis	Intent-to-treat
14.2.1.11.2	Sensitivity Analysis 4 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Tipping Point Analysis	Modified Intent-to-treat
14.2.1.12.1	Sensitivity Analysis 4 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Tipping Point Analysis	Intent-to-treat
14.2.1.12.2	Sensitivity Analysis 4 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Tipping Point Analysis	Modified Intent-to-treat

* Primary GSP endpoint is dependent on normality test results. If the normality is violated, the primary GSP endpoint will use ranked data. If the normality is not violated, the primary GSP endpoint will use continuous data.

Number	Title	Population
14.2.1.13.1	Sensitivity Analysis 5 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in each HDSM-Ax-7 Item from Baseline to End of Treatment - Multiple Imputation	Intent-to-treat
14.2.1.13.2	Sensitivity Analysis 5 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in each HDSM-Ax-7 Item from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.14.1	Sensitivity Analysis 5 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax 6-item Total from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.14.2	Sensitivity Analysis 5 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax 6-item Total from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.15.1	Site Poolability Analysis 1 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.15.2	Site Poolability Analysis 1 for HDSM-Ax: Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.1.16.1	Site Poolability Analysis 2 for HDSM-Ax: Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment with Analysis Center as a Random Effect - Multiple Imputations	Intent-to-treat
14.2.1.16.2	Site Poolability Analysis 2 for HDSM-Ax: Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment with Analysis Center as a Random Effect - Multiple Imputations	Modified Intent-to-treat
14.2.1.17.1	Site Poolability Analysis 3 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous][*] GSP from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.1.17.2	Site Poolability Analysis 3 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat

[*] Primary GSP endpoint is dependent on normality test results. If the normality is violated, the primary GSP endpoint will use ranked data. If the normality is not violated, the primary GSP endpoint will use continuous data.

Number	Title	Population
14.2.1.18.1	Site Poolability Analysis 4 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous]* GSP from Baseline to End of Treatment with Analysis Center as a Random Effect - Multiple Imputations	Intent-to-treat
14.2.1.18.2	Site Poolability Analysis 4 for GSP: ANCOVA Analysis of Change in [Ranked/Continuous] GSP from Baseline to End of Treatment with Analysis Center as a Random Effect - Multiple Imputations	Modified Intent-to-treat
14.2.2.1	Secondary Analysis 1: Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.2.2	Secondary Analysis 1: Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - No Imputation	Per-protocol
14.2.2.3	Secondary Analysis 1: Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.2.4	Secondary Analysis 2: Subjects Achieving ≥ 2-point improvement in HDSM-Ax-7 and 70% Reduction in GSP from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.2.5	Secondary Analysis 2: Subjects Achieving ≥ 2-point improvement in HDSM-Ax-7 and 70% Reduction in GSP from Baseline to End of Treatment - No Imputation	Per-protocol
14.2.2.6	Secondary Analysis 2: Subjects Achieving ≥ 2-point improvement in HDSM-Ax-7 and 70% Reduction in GSP from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat
14.2.2.7	Secondary Analysis 3: Subjects Achieving ≥ 1-point improvement in HDSM-Ax-7 and 50% Reduction in GSP from Baseline to End of Treatment - Multiple Imputations	Intent-to-treat
14.2.2.8	Secondary Analysis 3: Subjects Achieving ≥ 1-point improvement in HDSM-Ax-7 and 50% Reduction in GSP from Baseline to End of Treatment - No Imputation	Per-protocol
14.2.2.9	Secondary Analysis 3: Subjects Achieving ≥ 1-point improvement in HDSM-Ax-7 and 50% Reduction in GSP from Baseline to End of Treatment - Multiple Imputations	Modified Intent-to-treat

Number	Title	Population
14.2.3.1	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 by Visit	Intent-to-treat
14.2.3.2	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 by Visit	Per-protocol
14.2.3.3	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 by Visit	Intent-to-treat
14.2.3.4	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 by Visit	Per-protocol
14.2.3.5	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 and 70% Reduction in GSP by Visit	Intent-to-treat
14.2.3.6	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 and 70% Reduction in GSP by Visit	Per-protocol
14.2.3.7	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 and 50% Reduction in GSP by Visit	Intent-to-treat
14.2.3.8	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 and 50% Reduction in GSP by Visit	Per-protocol
14.2.3.9	Mean and Mean Change from Baseline in HDSM-Ax-7 by Visit	Intent-to-treat
14.2.3.10	Mean and Mean Change from Baseline in HDSM-Ax-7 by Visit	Per-protocol
14.2.3.11	Summary of Frequency of Missingness for HDSM-Ax-7	Intent-to-treat
14.2.3.12	Summary of Frequency of Missingness for HDSM-Ax-7	Per-protocol
14.2.3.13	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-11 by Visit	Intent-to-treat
14.2.3.14	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-11 by Visit	Per-protocol
14.2.3.15	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-11 by Visit	Intent-to-treat
14.2.3.16	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-11 by Visit	Per-protocol
14.2.3.17	Subjects Achieving ≥ 2-point improvement in HDSM-Ax-11 and 70% Reduction in GSP from Baseline to End of Treatment	Intent-to-treat
14.2.3.18	Subjects Achieving ≥ 2-point improvement in HDSM-Ax-11 and 70% Reduction in GSP from Baseline to End of Treatment	Per-protocol

Number	Title	Population
14.2.3.19	Subjects Achieving ≥ 1-point improvement in HDSM-Ax-11 and 50% Reduction in GSP from Baseline to End of Treatment	Intent-to-treat
14.2.3.20	Subjects Achieving ≥ 1-point improvement in HDSM-Ax-11 and 50% Reduction in GSP from Baseline to End of Treatment	Per-protocol
14.2.3.21	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-11 and 70% Reduction in GSP by Visit	Intent-to-treat
14.2.3.22	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-11 and 70% Reduction in GSP by Visit	Per-protocol
14.2.3.23	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-11 and 50% Reduction in GSP by Visit	Intent-to-treat
14.2.3.24	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-11 and 50% Reduction in GSP by Visit	Per-protocol
14.2.3.25	Mean and Mean Change from Baseline in HDSM-Ax-11 by Visit	Intent-to-treat
14.2.3.26	Mean and Mean Change from Baseline in HDSM-Ax-11 by Visit	Per-protocol
14.2.3.27	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax Question 4 by Visit	Intent-to-treat
14.2.3.28	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax Question 4 by Visit	Per-protocol
14.2.3.29	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax Question 4 by Visit	Intent-to-treat
14.2.3.30	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax Question 4 by Visit	Per-protocol
14.2.3.31	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax Question 5 by Visit	Intent-to-treat
14.2.3.32	Subjects Achieving ≥ 1-point Improvement in HDSM-Ax Question 5 by Visit	Per-protocol
14.2.3.33	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax Question 5 by Visit	Intent-to-treat
14.2.3.34	Subjects Achieving ≥ 2-point Improvement in HDSM-Ax Question 5 by Visit	Per-protocol
14.2.3.35	Subjects Achieving at least 70% Reduction in GSP by Visit	Intent-to-treat
14.2.3.36	Subjects Achieving at least 70% Reduction in GSP by Visit	Per-protocol
14.2.3.37	Subjects Achieving at least 50% Reduction in GSP by Visit	Intent-to-treat

Number	Title	Population
14.2.3.38	Subjects Achieving at least 50% Reduction in GSP by Visit	Per-protocol
14.2.3.39	Mean and Mean Change from Baseline in Ranked GSP by Visit	Intent-to-treat
14.2.3.40	Mean and Mean Change from Baseline in Ranked GSP by Visit	Per-protocol
14.2.3.41	Mean and Mean Change from Baseline in Absolute GSP by Visit	Intent-to-treat
14.2.3.42	Mean and Mean Change from Baseline in Absolute GSP by Visit	Per-protocol
14.2.3.43	Mean and Mean Percent Change from Baseline in GSP by Visit	Intent-to-treat
14.2.3.44	Mean and Mean Percent Change from Baseline in GSP by Visit	Per-protocol
14.2.3.45	Summary of Frequency of Missingness for GSP	Intent-to-treat
14.2.3.46	Summary of Frequency of Missingness for GSP	Per-protocol
14.2.3.47	Mean and Mean Change from Baseline in DLQI by Visit	Intent-to-treat
14.2.3.48	Meand and Mean Change from Baseline in DLQI by Visit	Per-protocol
14.2.3.49	Patient Global Impression of Severity (PGI-S) by Visit	Intent-to-treat
14.2.3.50	Patient Global Impression of Severity (PGI-S) by Visit	Per-protocol
14.2.3.51	Patient Global Impression of Change (PGI-C) at End of Treatment	Intent-to-treat
14.2.3.52	Patient Global Impression of Change (PGI-C) at End of Treatment	Per-protocol
14.2.3.53	Subgroup Analysis: Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations – by Age Group Group	Intent-to-treat
14.2.3.54	Subgroup Analysis: Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations – by Gender	Intent-to-treat
14.2.3.55	Subgroup Analysis: Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations – by Ethnicity	Intent-to-treat
14.2.3.56	Subgroup Analysis: Subjects Achieving ≥2-point Improvement in HDSM-Ax-7 from Baseline to End of Treatment - Multiple Imputations – by Race	Intent-to-treat
14.2.3.57	Subgroup Analysis: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment -- Multiple Imputations – by Age Group	Intent-to-treat

Number	Title	Population
14.2.3.58	Subgroup Analysis: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment -- Multiple Imputations – by Gender	Intent-to-treat
14.2.3.59	Subgroup Analysis: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment -- Multiple Imputations – by Ethnicity	Intent-to-treat
14.2.3.60	Subgroup Analysis: ANCOVA Analysis of Change in Continuous GSP from Baseline to End of Treatment -- Multiple Imputations – by Race	Intent-to-treat
14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	Safety
14.3.1.2.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety

Number	Title	Population
14.3.1.2.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.2.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 8) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety

Number	Title	Population
14.3.1.3.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 6 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.3.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 5 (Day 15) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety

Number	Title	Population
14.3.1.4.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.4.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 7 (Day 22) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety

Number	Title	Population
14.3.1.5.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.5.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 8 (Day 29) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety

Number	Title	Population
14.3.1.6.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.6.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 9 (Day 36) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety

Number	Title	Population
14.3.1.7.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.7.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 12 (Day 48, EOT) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.1	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.2	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.3	Number and Percentage of Subjects with Serious Treatment-Related Treatment-Emergent Adverse Events Cumulative Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.4	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.5	Number and Percentage of Subjects with Severe Treatment-Emergent Adverse Events Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Dose Interruption Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Leading to Study Discontinuation Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.8	Number and Percentage of Subjects with Treatment-Emergent Adverse Events of Special Interest	Safety

Number	Title	Population
	Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	
14.3.1.8.9	Number and Percentage of Subjects with Anticholinergic Treatment-Emergent Adverse Events Cumulative to Visit 13 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.8.10	Number and Percentage of Subjects with Local Site Reaction Treatment-Emergent Adverse Events Cumulative to Visit 14 (Day 57, Follow-up) by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.1.9	Summary of Subjects with Allergic Contact Dermatitis	Safety
14.3.4.1	Mean and Mean Change from Baseline in Serum Biochemistry Values by Visit	Safety
14.3.4.2	Mean and Mean Change from Baseline in Hematology Values by Visit	Safety
14.3.4.3	Mean and Mean Change from Baseline in Continuous Urinalysis Values by Visit	Safety
14.3.4.4	Categorical Urinalysis Values by Visit	Safety
14.3.5	Study Drug Administration Exposure and Compliance	Safety
14.3.6.1	Worst Post-baseline Severity for Local Tolerability Assessments by Treatment Group	Safety
14.3.6.2	Worst Severity for Local Tolerability Assessments by Treatment Group and Visit	Safety
14.3.6.3	Shift in Worst Severity for Local Tolerability Assessments from Baseline to Each Visit	Safety
14.3.6.4	Mean and Mean Change from Baseline in Vital Signs Values by Visit	Safety
14.3.6.5	Summary of Concomitant Medications by Drug Class and Generic Drug Name	Safety

16. LIST OF PLANNED FIGURES

Number	Title	Population
14.2.1	LS Mean Proportion of Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 by Visit -- Bar Chart	Intent-to-Treat
14.2.2	LS Mean Proportion of Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-7 by Visit -- Bar Chart	Per-protocol
14.2.3	LS Mean Proportion of Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-11 by Visit -- Bar Chart	Intent-to-Treat
14.2.4	LS Mean Proportion of Subjects Achieving ≥ 1-point Improvement in HDSM-Ax-11 by Visit -- Bar Chart	Per-protocol
14.2.5	LS Mean Proportion of Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 by Visit -- Bar Chart	Intent-to-Treat
14.2.6	LS Mean Proportion of Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-7 by Visit -- Bar Chart	Per-protocol
14.2.7	LS Mean Proportion of Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-11 by Visit -- Bar Chart	Intent-to-Treat
14.2.8	LS Mean Proportion of Subjects Achieving ≥ 2-point Improvement in HDSM-Ax-11 by Visit -- Bar Chart	Per-protocol
14.2.9	LS Mean Proportion of Subjects Achieving ≥ 1-point Improvement in HDSM-Ax Question 4 by Visit -- Bar Chart	Intent-to-Treat
14.2.10	LS Mean Proportion of Subjects Achieving ≥ 1-point Improvement in HDSM-Ax Question 4 by Visit -- Bar Chart	Per-protocol
14.2.11	LS Mean Proportion of Subjects Achieving ≥ 2-point Improvement in HDSM-Ax Question 5 by Visit -- Bar Chart	Intent-to-Treat
14.2.12	LS Mean Proportion of Subjects Achieving ≥ 2-point Improvement in HDSM-Ax Question 5 by Visit -- Bar Chart	Per-protocol
14.2.13	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 2-point Improvement in HDSM-Ax-7 and 70% Reduction in GSP by Visit -- Bar Chart	Intent-to-Treat
14.2.14	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 2-point Improvement in HDSM-Ax-7 and 70% Reduction in GSP by Visit -- Bar Chart	Per-protocol
14.2.15	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 2-point Improvement in HDSM-Ax-11 and 70% Reduction in GSP by Visit -- Bar Chart	Intent-to-Treat
14.2.16	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 2-point Improvement in HDSM-Ax-11 and 70% Reduction in GSP by Visit -- Bar Chart	Per-protocol

Number	Title	Population
14.2.17	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 1-point Improvement in HDSM-Ax-7 and 50% Reduction in GSP by Visit -- Bar Chart	Intent-to-Treat
14.2.18	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 1-point Improvement in HDSM-Ax-7 and 50% Reduction in GSP by Visit -- Bar Chart	Per-protocol
14.2.19	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 1-point Improvement in HDSM-Ax-11 and 50% Reduction in GSP by Visit -- Bar Chart	Intent-to-Treat
14.2.20	LS Mean Proportion of Subjects Achieving Composite Endpoint Response of ≥ 1-point Improvement in HDSM-Ax-11 and 50% Reduction in GSP by Visit -- Bar Chart	Per-protocol
14.2.21	LS Mean Change from Baseline in HDSM-Ax-7 by Visit -- Line Graph	Intent-to-Treat
14.2.22	LS Mean Change from Baseline in HDSM-Ax-7 by Visit -- Line Graph	Per-protocol
14.2.23	LS Mean Change from Baseline in HDSM-Ax-11 by Visit -- Line Graph	Intent-to-Treat
14.2.24	LS Mean Change from Baseline in HDSM-Ax-11 by Visit -- Line Graph	Per-protocol
14.2.25	LS Mean Proportion of Subjects Achieving 70% Reduction in GSP by Visit -- Bar Chart	Intent-to-Treat
14.2.26	LS Mean Proportion of Subjects Achieving 70% Reduction in GSP by Visit -- Bar Chart	Per-protocol
14.2.27	LS Mean Proportion of Subjects Achieving 50% Reduction in GSP by Visit -- Bar Chart	Intent-to-Treat
14.2.28	LS Mean Proportion of Subjects Achieving 50% Reduction in GSP by Visit -- Bar Chart	Per-protocol
14.2.29	LS Mean Change from Baseline in Rank-based GSP by Visit -- Line Graph	Intent-to-Treat
14.2.30	LS Mean Change from Baseline in Rank-based GSP by Visit -- Line Graph	Per-protocol
14.2.31	LS Mean Change from Baseline in Absolute GSP by Visit -- Line Graph	Intent-to-Treat
14.2.32	LS Mean Change from Baseline in Absolute GSP by Visit -- Line Graph	Per-protocol
14.2.33	LS Mean Percent Change from Baseline in GSP by Visit -- Line Graph	Intent-to-Treat
14.2.34	LS Mean Percent Change from Baseline in GSP by Visit -- Line Graph	Per-protocol
14.2.35	LS Mean Change from Baseline in DLQI Score by Visit -- Line Graph	Intent-to-Treat
14.2.36	LS Mean Change from Baseline in DLQI Score by Visit -- Line Graph	Per-protocol

Number	Title	Population
14.2.37	Normality Test Results for GSP	Intent-to-Treat
14.2.38	Plot of GSP Outliers	Intent-to-Treat
14.2.39	Patient Global Impression – Severity (PGI-S) by Visit	Intent-to-Treat
14.2.40	Patient Global Impression – Severity (PGI-S) by Visit	Per Protocol
14.3.1.1.1	Number of Subjects with Study Discontinuation due to Treatment-Emergent Adverse Events by Time on Treatment	Safety
14.3.1.1.2	Number of Subjects with Study Discontinuation due to Anticholinergic Treatment-Emergent Adverse Events by Time on Treatment	Safety
14.3.1.1.3	Number of Subjects with Study Discontinuation due to Treatment-Emergent Adverse Events of Special Interest by Time on Treatment	Safety
14.3.1.1.4	Number of Treatment-Related Treatment-Emergent Adverse Events over Time	Safety
14.3.1.1.5	Number of Subjects with any Treatment-Related Treatment-Emergent Adverse Event over Time	Safety
14.3.1.1.6	Number of Local Site Reaction Treatment-Emergent Adverse Events over Time	Safety
14.3.1.1.7	Number of Subjects with any Local Site Reaction Treatment-Emergent Adverse Event over Time	Safety
14.3.1.2	Summary of Local Tolerability by Severity from Baseline to Day 43 (EOT)	Safety

17. LIST OF PLANNED DATA LISTINGS

Number	Title	Population
14.3.2.1	Serious Adverse Events	Safety
14.3.2.2	Adverse Events Resulting in Study Discontinuation	Safety
14.3.2.3	Adverse Events Resulting in Death	Safety
16.2.1	Subject Disposition	All Randomized
16.2.2	Protocol Deviations	Safety
16.2.3	Analysis Populations	All Randomized
16.2.4.1	Demographic and Baseline Characteristics	All Randomized
16.2.4.2	Medical History	Safety
16.2.4.3	Prior and Concomitant Medications	Safety
16.2.5.1	Study Medication Dosing and Compliance	Safety
16.2.5.2	Study Drug Accountability	Safety
16.2.5.3	Exposure Parameters	Safety
16.2.6.1	Hyperhidrosis Disease Severity Measure - Axillary Results	All Randomized
16.2.6.2	Gravimetric Sweat Production	All Randomized
16.2.6.3	Dermatology Quality of Life Index Results	All Randomized
16.2.7.1	All Adverse Events	Safety
16.2.7.2	Adverse Events of Special Interest	Safety
16.2.7.3	Anticholinergic Adverse Events	Safety
16.2.7.4	Screening Period Adverse Events	Safety
16.2.7.5	Subjects with Treatment-Emergent Allergic Contact Dermatitis	Safety
16.2.8.1	Serum Biochemistry Results	Safety
16.2.8.2	Hematology Results	Safety
16.2.8.3	Urinalysis Results	Safety
16.2.8.4	Pregnancy Results	Safety
16.2.9.1	Local Tolerability Results	Safety
16.2.9.2	Vital Signs Results	Safety
16.2.9.3	Physical Examination Results	Safety
16.2.9.4	Prior or Concomitant Therapies or Procedures	Safety
16.2.10	Subject Study Visits	All Randomized

18. APPENDICES

18.1 Schedule of Events

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

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13
PROCEDURE	**Screening**			**Rescreening / Baseline**								**End of Treatment**	**Follow-up**
Gravimetric Timepoint		**GSP 1[1]**	**GSP 2[1]**	**GSP 3[1]**						**GSP 4**	**GSP 5**	**GSP 6**	
Day (allowable window)	***Up to 31 days prior to GSP1***			***(Day 1)***	**Day 8 (± 2)**	**Day 15 (± 2)**	**Day 22 (± 2)**	**Day 29 (± 2)**	**Day 36 (± 2)**	**Day 41 (±2)**	**Day 42 (± 2)**	**Day 43 (± 2)**	**Day 57 (± 3)**
Optional End of Study Patient Survey[13]													**X**

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

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

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

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

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

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

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

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

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

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

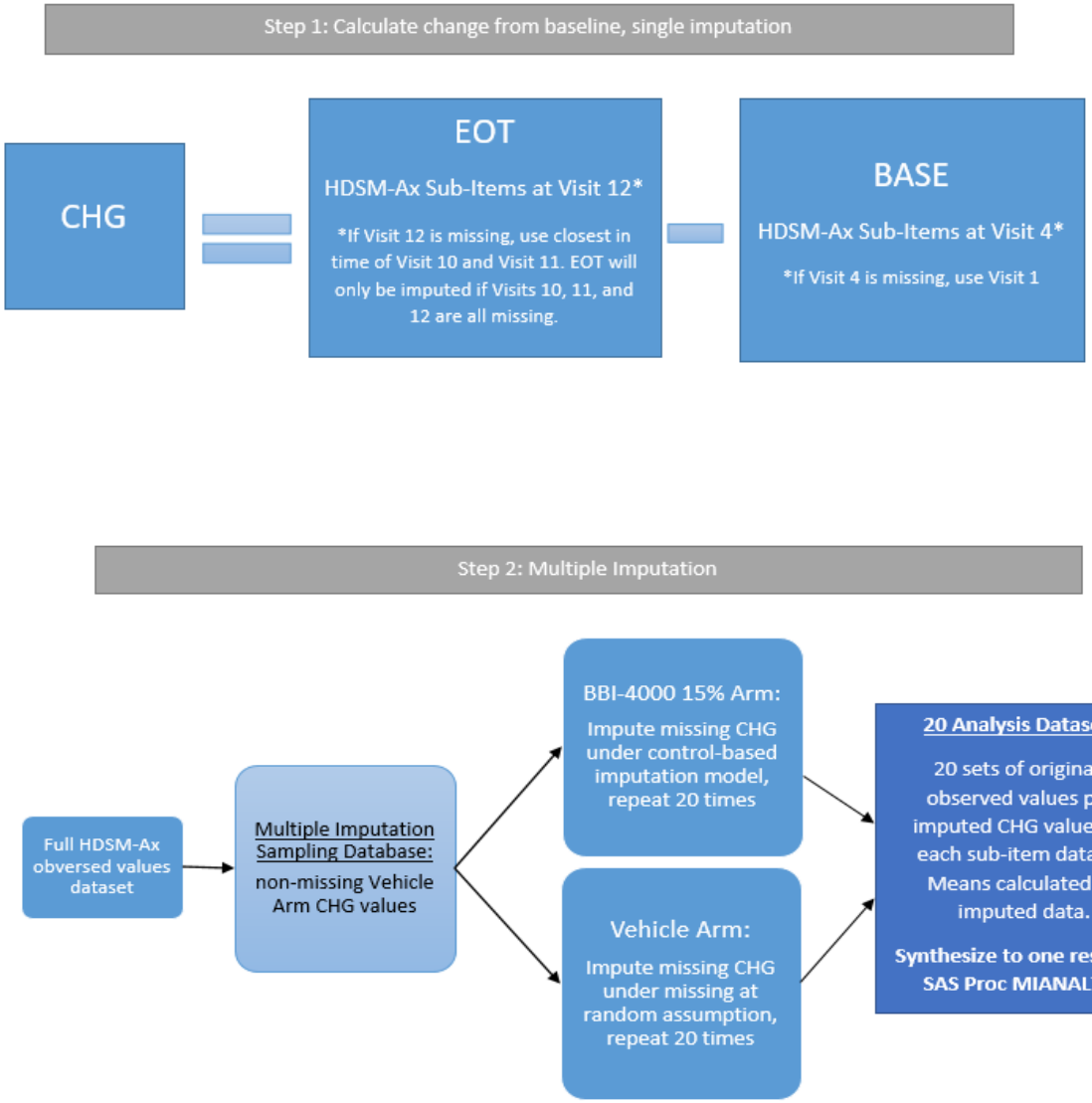
[10] Pump container 1 of 2 to be primed, weighed, and dispensed to subject at Baseline (Visit 4). Pump 2 of 2 to be primed, weighed, and dispensed to subject at Day 22 (Visit 7). Written instructions for nightly dosing will be given to the subject. Subjects will apply their first dose of gel prior to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

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

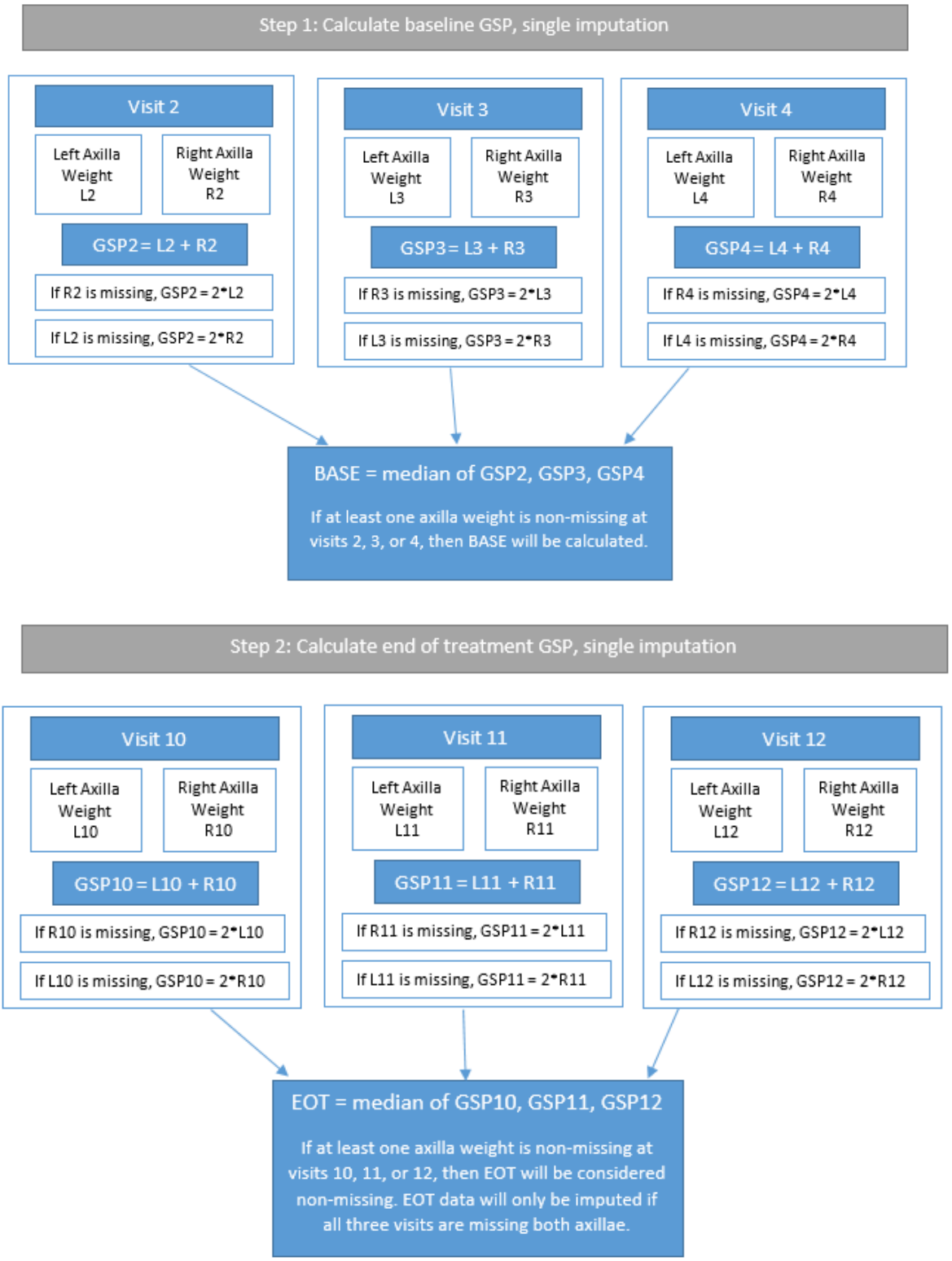
[12] FOCBP for this study includes any premenopausal female capable of becoming pregnant who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [≥6 months prior to baseline], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive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

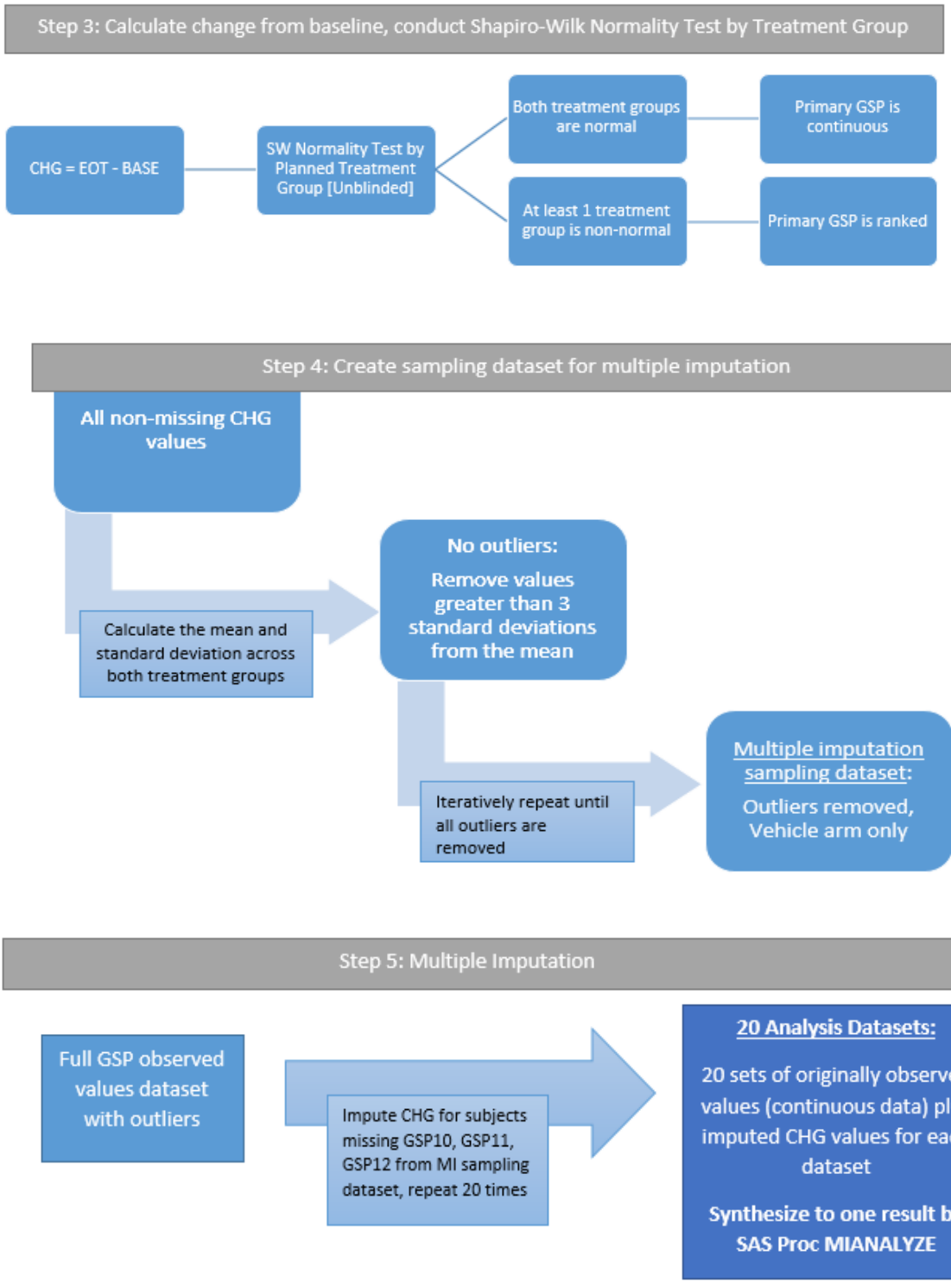
[13] Optional end of study survey will be offered to subjects ≥ 17 years of age.

18.2 HDSM-Ax Imputation Flow Chart



18.3 GSP Imputation Flow Chart




Step 3: Calculate change from baseline, conduct Shapiro-Wilk Normality Test by Treatment Group
CHG = EOT - BASE
SW Normality Test by Planned Treatment Group [Unblinded]
Both treatment groups are normal
Primary GSP is continuous
At least 1 treatment group is non-normal
Primary GSP is ranked
Step 4: Create sampling dataset for multiple imputation
All non-missing CHG values
Calculate the mean and standard deviation across both treatment groups
No outliers:
Remove values greater than 3 standard deviations from the mean
Iteratively repeat until all outliers are removed
Multiple imputation sampling dataset:
Outliers removed, Vehicle arm only
Step 5: Multiple Imputation
Full GSP observed values dataset with outliers
Impute CHG for subjects missing GSP10, GSP11, GSP12 from MI sampling dataset, repeat 20 times
20 Analysis Datasets:
20 sets of originally observed values (continuous data) plus imputed CHG values for each dataset
Synthesize to one result by SAS Proc MIANALYZE

19. ATTACHMENTS

None.