16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

Final SAP, Version 1.0, dated 13 Sep 2024

Statistical Analysis Plan

A Phase 2a, Multicenter, Proof-of-Concept Clinical Trial to Evaluate Efficacy and Safety of BSI-045B mAb Injection as Monotherapy in Patients with Moderate to Severe Atopic Dermatitis

Protocol Number	BSI-045B-002
Investigational Product:	BSI-045B
Sponsor:	Biosion, Inc.
Statistical Analysis Institution:	Acumen Medical Information & Technology Co., Ltd.
Version No.:	V1.0
Version Date:	September 13, 2024

Signature Page for Approval

The following signers approved the Statistical Analysis Plan:

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Version History

Version	Date	Description of Changes
1.0	September 13, 2024	Original Document.

Abbreviations

AD	Atopic Dermatitis
ADA	Antidrug Antibody
AE	Adverse Events
ATC	Anatomic Therapeutic Chemical Classification
AUC	Area Under the Serum Drug Concentration-time Curve
BMI	Body Mass Index
CI	Confident Interval
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
EASI	Eczema Area and Severity Index
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICH	International Conference of Harmonization
IGA	Investigator's Global Assessment
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetics
PP-NRS	Peak Pruritus Numerical Rating Scale
PT	Preferred Term
Q2W	Every 2 Weeks
QW	Every Week
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHODrug	World Health Organization Drug Dictionaries

1. Introduction

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data from the BSI-045B-002 study.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. In addition, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data.

2. Project Overview

2.1 Study Design

The study design is presented in the Schema. The study is a multicenter clinical trial and is designed as a proof-of-concept study to evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD of BSI-045B following SC injections.

The present study, which is intended to assess the efficacy and safety of BSI-045B in moderate to severe AD patients, is being conducted as a proof-of-concept study prior to performing a more traditional Phase 2 trial. If this study is successful, the Sponsor plans to conduct a future Phase 2b, randomized, blinded, dose-finding trial that will formally compare BSI-045B with placebo and/or other treatments for AD.

The study will enroll patients with moderate to severe AD. Eligible patients will receive BSI-045B 300 mg treatment, firstly at every week (QW) during Week 1 to Week 4, and then every 2 weeks (Q2W) to Week 24.

Patients will start with a washout period for anti-AD treatment prior to study treatment, including systemic and topical agents and phototherapy. The duration of the washout period varies by therapy and the Investigator should consult section 7.2 in the protocol. Eligible patients who complete the washout period for previous therapies for AD will be treated with BSI-045B as described above.

Monitoring by Safety Steering Committee (SSC)

The SSC will monitor the study and will be composed of representatives from the Sponsor, the National Principal Investigator, and independent physicians, as indicated in the SSC charter. The SSC will formally assess safety findings when 20 patients complete dosing at Week 12. The SSC will assess all events, especially treatment-related SAEs that might prompt a change to the study.

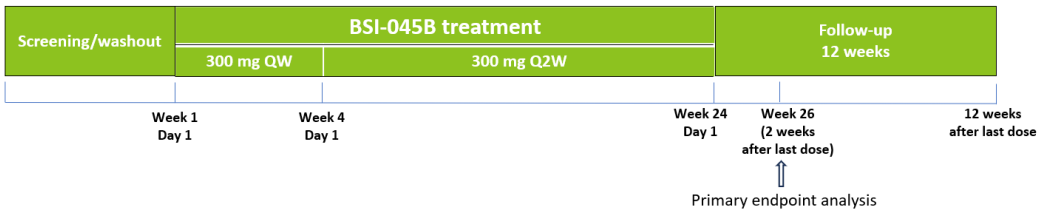
Assessment of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients with ⩾EASI75 at Week 26 (2 weeks after last dose at Week 24).

Follow-up Period

After the Treatment Period, there will be a 12 -week Follow-up Period.

SCHEMA: BSI-045B-002 Study Design



2.2 Study Objectives & Endpoints

Objectives and endpoints for this study are detailed in Table 1.

Table 1: Objectives and Endpoints in BSI-045B-002 Study

Objectives	Endpoints
Primary	
Primary Efficacy Objective: To evaluate the efficacy of BSI-045B in patients with moderate to severe atopic dermatitis (AD)	**Primary Efficacy Endpoint**: Proportion of patients with ≥Eczema Area and Severity Index (EASI)75 at Week 26 (2 weeks after last dose at Week 24)
Primary Safety Objective: To evaluate the safety and tolerability of BSI-045B in patients with moderate to severe AD	**Primary Safety Endpoint**: Safety and tolerability as evidenced by the incidence of adverse events (AEs), anti-BSI-045B antidrug antibody (ADA) formation, clinical laboratory evaluations, 12-lead electrocardiography (ECGs), vital signs, and physical examinations. The relationships between study drugs and AEs will be evaluated by the Investigators.
Secondary	
To evaluate the pharmacokinetics (PK) of BSI-045B	Pharmacokinetics listings will be provided. PK parameters might be estimated through compartmental modeling. Additionally, the PK/Efficacy relationship might be explored.
To evaluate the immunogenicity of BSI-045B	Anti-BSI-045B ADA during and post BSI-045B treatment
Exploratory	
To assess additional efficacy and safety outcomes of BSI-045B	➢ Proportion of patients with EASI90 at Week 26 (2 weeks after last dose at Week 24) ➢ Proportion of patients with EASI50 at Week 26 (2 weeks after last dose at Week 24) ➢ Percent change from baseline in EASI at each visit ➢ Proportion of patients achieving Investigator's Global Assessment (IGA) 0 or 1 at 26 (2 weeks after last dose at Week

	24) ➢ Percent changes in PP-NRS scores at Week 26 (2 weeks after last dose at Week 24) ➢ Proportion of patients achieving Facial IGA 0/1 at Week 26 (2 weeks after last dose at Week 24) ➢ Occurrence of conjunctivitis
To evaluate the PD biomarkers of BSI-045B	Serum levels of thymus and activation regulated chemokine/C-C chemokine ligand 17 (TARC/CCL-17), periostin, and IgE during and post BSI-045B treatment

AD = atopic dermatitis; ADA = antidrug antibody; AE = adverse event; CCL-17 = C-C chemokine ligand 17; EASI = Eczema Area and Severity Index; ECG = electrocardiography; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; PD = pharmacodynamic; PK = pharmacokinetic; PP-NRS = Peak Pruritus Numerical Rating Scale; TARC = thymus and activation regulated chemokine

2.3 Sample Size

With a minimum sample size of 20 patients, the maximum one-sided 95% confidence interval width for the proportion achieving EASI75 equals 21%.

With a maximum sample size of 24 patients, the maximum one-sided 95% confidence interval width for the proportion achieving EASI75 equals 19%.

3. Analysis Population

The statistical analysis sets involved in this study are as follows:

Enrolled Population: including all subjects who sign informed consent form and are successfully screened.

Safety Analysis Set: including all the subjects who received at least one dose of the study drug. This analysis set will be used for analysis of safety endpoint.

Efficacy Analysis Set: including all the subjects who received at least one dose of the study drug and have undergone at least one post-baseline efficacy assessment. This analysis set will be used for analysis of efficacy endpoint.

Per protocol analysis set: a subset of efficacy analysis set of patients without any importance protocol violation, as defined by the sponsor prior to the data base locked (adhere to ICH E3 guidance) Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

4. Statistical Analysis

4.1 General Considerations for Statistical Analysis

4.1.1 General Rules

No statistical hypothesis testing or inferential analyses are planned. The general analytical approach for all endpoints will be descriptive in nature.

Continuous variables (such as age) will be summarized with the observed number, mean, median, standard deviation, minimum, and maximum; categorical variables will be summarized with frequency and percentage of each category.

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data; the mean, median, and percentiles will be presented to 1 extra decimal place compared to the raw data; and the standard deviation will be displayed to 2 extra decimal places compared to the raw data. The maximum number of decimal places is 3

and values will be truncated to 3 decimal places in situations where there are more than 3 decimal places. Frequency tabulations will be presented by number and percentage, where the percentage is presented in parenthesis to 1 decimal place.

4.1.2 Baseline Definition and Change from Baseline and Percent Change from Baseline

Baseline data are defined as last non-missing assessment which are collected prior to or on the day of first dose, and must be prior to the administration of first dose, including scheduled and unscheduled visits, unless otherwise specified. Hence, change from baseline = post-baseline value – baseline value. Percent change from baseline = (post-baseline value – baseline value)/ baseline value×100%.

4.1.3 Study Day

If the date of assessment occurs on or after the first dose date, then study day will be calculated as (date of assessment - date of first dose) + 1. If the date of assessment occurs prior to the first dose date, then study day will be calculated as date of assessment - date of first dose. There is no study day 0.

4.1.4 Visit Window

The nominal visit as defined in protocol and recorded on the Case Report Form (CRF) will be used in the statistical analyses unless other specified. Regarding efficacy endpoints, the analysis visit during follow-up period will be dynamically derived. For instance, if the subject finished the last dosing visit at Week 14, the first follow-up visit (i.e. FU1) will be set as the first visit after Week 14 (i.e. Week16) and subsequent follow-up visits will be derived accordingly as Week18, Week20, Week 22, Week24, and Week 26. Unscheduled data will not be windowed into planned analysis visits for summary tables but will be included in overall post-baseline summaries, such as worst or last values.

In addition, unscheduled data will be listed and may be plotted in figures based on study days.

4.1.5 Missing Data

Unless otherwise specified, missing data will be treated as missing, ie, no special handling will be performed. For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Details of efficacy and safety data handling will be documented in efficacy and safety analyses section.

4.1.6 Partial/Missing Dates

For partial dates, the algorithms for imputation will vary depending upon the parameter; missing or incomplete medications start and stop dates will be imputed to determine

whether the medications are taking concomitantly. Missing AE start dates will be imputed to determine whether the adverse events are treatment emergent. In listings, all dates will be listed as recorded. The details of imputation rules can be found in Appendix 1.

4.2 Disposition of Subjects

The number and percentage of subjects in the following disposition categories will be summarized:

- Subjects signed the informed consent
- Subjects screen failure and reason for screen failure
- Subjects enrolled
- Subjects received study drug
- Subjects completed/discontinued treatment and reason for discontinuation
- Subjects completed/discontinued study and reason for discontinuation

The number and percentage of subjects in each analysis set and reasons for exclusion from an analysis set will be summarized in all subjects.

A listing of subject disposition based on all subjects will be provided.

4.3 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol.

An important protocol deviation is defined as a protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

A summary of the number and percentage of subjects with important protocol deviations by type of deviation will be provided in safety analysis set.

A listing of all protocol deviations will be provided by subject number.

4.4 Demographics and Baseline Information

Demographics and baseline information analysis will be summarized in safety analysis set.

4.4.1 Demographics

Descriptive statistics will be performed for demographic variables. The following information will be tabulated and summarized.

- Age (years) = Integer of [(Date of Signature of the Informed Consent - Date of Birth + 1)/365.25].

- Gender: Male and Female
- Race: White, American Indian or Alaska Native, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, and Other
- Height (cm)
- Body Weight (kg)
- Body Mass Index (BMI) (kg/m^2) = weight (kg)/height $(m)^2$
- Smoking History: Current, Former, Never
- Alcohol History: Current, Former, Never

The demographics list will be provided subject number.

4.4.2 Drug Abuse, Donation History and Allergy History

Drug abuse, donation history and allergy history will be listed by subject number.

4.4.3 Assessment of Suicidality (PH-2)

Assessment of suicidality (PH-2) will be listed subject number.

4.4.4 Medical history

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 27.0 or higher and tabulated by system organ class (SOC), preferred term (PT). Subjects with multiple medical histories in the same SOC or PT are counted only once for the respective SOC or PT.

Summaries are ordered in decreasing frequencies order of SOC and then, within an SOC, in decreasing frequencies by PT. If the frequencies tie, an alphabetic order will be applied.

All medical history will be listed by subject number.

4.4.5 Baseline Disease Characteristics

Duration of AD disease and baseline atopic dermatitis severity will be summarized descriptively.

Duration of AD disease (months) = (date of first dose - date of first diagnosis + 1)/30.4375, rounded to the one decimal place.

Baseline Eczema Area and Severity Index (EASI) score will be summarized descriptively.

Baseline Global Assessment of Disease Severity (IGA) score will be tabulated, and the subject number and percentage for the score will be presented.

Baseline Peak Pruritus Numerical Rating Scale (PP-NRS) score will be summarized descriptively. The baseline PP-NRS score is based on the average of daily PP-NRS

scores for the 7 days immediately preceding Day 1. In order to calculate an average for the score, the subject must have completed the diary for a minimum of 4 days during the previous 7 days.

Baseline conjunctivitis assessment is defined as the assessment on Day 1. The percentage of subjects with/without conjunctivitis at baseline will be tabulated.

Baseline total Body Surface Area (BSA) affected by AD will be summarized descriptively.

Baseline disease characteristics will be listed by subject number.

4.5 Prior and Concomitant Medications

Prior and concomitant drug name will be coded using World Health Organization Drug (WHODrug) dictionary version Global B3 March 1, 2023 or higher and will be summarized by Anatomical Therapeutic Classification (ATC) therapeutic group (i.e., ATCII), Preferred Term Title (PTT) in safety analysis set. At each level of summarization, frequency and percentage of subjects will be displayed and a subject is counted once if he/she reports one or more medications at that level.

Prior medications are defined as medications that stopped before the date and time of the first dose; concomitant medications are defined as medications that are ongoing at the first dose or start after the first dose. Medications with missing start and/or stop dates will be imputed to determining whether it is concomitant. If it is impossible to determine the prior or concomitant status, it will be summarized as concomitant medications.

A listing of all prior and concomitant medications will be provided by subject number.

4.6 Prior and Concomitant Non-Medication Therapy

Prior and concomitant non-drug treatment will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 27.0 or higher and tabulated by SOC, PT in safety analysis set.

A listing of all prior and concomitant non-medication therapy will be provided.

4.7 Efficacy Analysis

Efficacy analysis will be summarized in efficacy analysis set. As a sensitivity analysis, the per protocol population will also be assessed.

4.7.1 Eczema Area and Severity Index (EASI)

The EASI score is a composite index that measures the severity of AD based on the average intensity of four clinical signs (erythema, edema/papulation, excoriations, and lichenification) at four body areas (head, neck, upper extremities, and trunk and lower extremities), and the percentage of affected area for each of the four body areas.

The baseline for EASI is defined as the score measured prior to dosing on Day 1.

Measured values, changes from baseline and percent change from baseline in EASI score will be summarized descriptively on scheduled visit.

The primary efficacy endpoint is the proportion of subjects with EASI75 (a 75% reduction in the EASI score) at 2 weeks after last dose at Week 24. The exploratory endpoints include the proportion of subjects achieving EASI90 at Weeks 26 (2 weeks after last dose at Week 24), the proportion of patients with EASI50 at Week 26 (2 weeks after last dose at Week 24). The corresponding 95% two-sided confidence intervals (CIs) will be calculated using the exact binomial distribution and presented for EASI75, EASI90, and EASI50.

For primary analysis, the percent change from baseline in EASI score, EASI50, EASI75, EASI90 in the EASI score will be calculated with observed data. If the subject has missing value for EASI at scheduled visit, the subject will be excluded from the calculation of proportion at specify visit.

Mean (±standard deviation) of the percent change from baseline in EASI score with observed data will be plotted at scheduled visit.

For sensitivity analysis, the missing value will also be imputed with last observation carried forward (LOCF) method. The imputed data for the percent change from baseline in EASI score will be summarized descriptively on scheduled visit. The proportion of subjects with EASI50, EASI75 and EASI90 at 2 weeks after last dose at Week 26 will also be calculated with imputed data.

A listing of all EASI score will be provided by subject number.

4.7.2 Investigator's Global Assessment of Disease Severity (IGA)

The IGA requires the investigator to rate the severity of AD on a scale from 0 (clear) to 4 (severe).

The baseline for IGA is defined as the score measured on Day 1.

Proportion of subjects achieving an IGA response (IGA = 0 [clear] or IGA = 1 [almost clear] on a scale of 0–4, where 4 represents severe atopic dermatitis) at 2 weeks after last dose at Week 24 with observed data will be presented. If the subject has missing value for IGA at scheduled visit, the subject will be excluded from the calculation of proportion at specify visit. The corresponding 95% two-sided confidence intervals (CI), calculated using the exact binomial distribution, will also be presented.

A listing of all IGA result will be provided by subject number.

4.7.3 Peak Pruritus Numerical Rating Scale (PP-NRS)

The assessment tool for itching is the PP-NRS, on which the subject rates the maximum severity of the itch from AD on a scale from 0 (no itch) to 10 (worst itch imaginable) over a 24-hour period. The baseline PP-NRS score is based on the average of daily PP-

NRS scores for the 7 days immediately preceding Day 1. In order to calculate an average for the score, the subject must have completed the diary for a minimum of 4 days during the previous 7 days.

Measured values, changes from baseline and percent change from baseline in PP-NRS score will be summarized descriptively at 2 weeks after last dose at Week 24.

The PP-NRS score at Week 26 (2 weeks after last dose at Week 24) is based on the average of the first consecutively 7 days recorded on visit of FU2, as the PP-NRS score for a treatment cycle will be collected at the next visit.

Mean (±standard deviation) of percent change from baseline of PP-NRS score with observed data will be plotted at scheduled visit.

A listing of all PP-NRS score will be provided by subject number.

4.7.4 Facial IGA Assessment

Facial IGA assessment will be summarized with the same method of Investigator's Global Assessment (IGA).

4.8 Safety Analysis

The safety analysis will be summarized in safety analysis set.

4.8.1 Drug Exposure and Compliance Analysis

Below parameters will be presented for BSI-045B:

- Number of injections received
- Duration of exposure (weeks)
- Total protocol-planned dose (mg)
- Total administered dose (mg)
- Actual dose intensity (mg/week) for loading dose
- Actual dose intensity (mg/week) for maintenance dose
- Relative dose intensity (%)
- Number of subjects with dose missed and reason for dose missed
- Number of subjects with dose changed and reason for dose changed
- Number of subjects with injection interrupted and reason for injection interrupted

Duration of exposure (weeks) = (Date of last study drug injection – date of first study drug injection + 14 days) / 7.

Total protocol-planned dose (mg) for BSI-045B = 300 mg QW×4 times + 300mg Q2W×10 times = 4200mg

Total administered dose (mg) = Sum of doses administered for both loading dose and maintenance dose.

Actual dose intensity (mg/week) for loading dose = Sum of doses administered (mg) /duration of exposure (weeks) in loading dose period.

Actual dose intensity (mg/week) for maintenance dose = Sum of doses administered (mg) /duration of exposure (weeks) in maintenance dose period.

Relative dose intensity (%) for BSI-045B = Total administered dose (mg) / Total protocol-planned dose (mg)*100%.

In addition, the Relative dose intensity (%) for BSI-045B will be categorized to the groups: <50%, 50% to <70%, 70% to <90%, 90% to <110%, >=110%.

4.8.2 Adverse Events

Adverse events will be coded using the MedDRA dictionary version 27.0 or higher. The severity of the toxicities will be graded according to the NCI CTCAE version 5.0.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study drug.

TEAEs will be summarized by system organ class (SOC) and preferred term (PT) in descending order of frequency. For each TEAE, the percentage of participants who experience at least 1 occurrence of given event will be summarized.

Causal relationship and toxicity grade are required entries on the adverse events eCRF, so missing data are not expected. However, any AEs with missing causal relationships will be imputed as ‘Related’ and any missing toxicity grades will be imputed to grade 3 for summary but still keep missing in listing.

A subject with more than one occurrence of the same adverse event in a particular system organ class will be counted only once in the total of those experiencing adverse events in that particular system organ class. If a subject experience the same adverse event at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence.

The numbers of subjects and incidence rate for all TEAEs, TEAEs of BSI-045B-related for following category will be tabulated:

1) Overview of TEAEs
2) TEAEs by SOC and PT
3) TEAEs by SOC and PT and by Maximum NCI CTCAE grade
4) Serious TEAEs by SOC and PT
5) Grade>=3 TEAEs by SOC and PT
6) TEAEs Leading to BSI-045B Interruption by SOC and PT

7) TEAEs Leading to BSI-045B Withdrawn by SOC and PT

8) TEAEs Leading to Death by SOC and PT

The following AE listings of all subjects will be provided.

1) All AEs
2) BSI-045B Related AEs
3) Serious AEs
4) AEs Leading to BSI-045B Withdrawn
5) AEs Leading to Death

4.8.3 Clinical laboratory Tests

Clinical laboratory tests include hematology, chemistry, coagulation and urinalysis.

Laboratory parameters with numeric value and their change from baseline will be summarized descriptively on scheduled visit, minimum post-baseline value and maximum post-baseline value.

A listing of clinically significant abnormal values (including all abnormal values at scheduled visits and unscheduled visits) will be provided by subject number.

Urine and blood pregnancy test results will be listed only by subject number.

4.8.4 Vital Signs

For parameters of vital signs, measured values and changes from baseline will be summarized descriptively on scheduled time point, minimum post-baseline value and maximum post-baseline value.

A listing for all parameter values of vital signs, and for marked abnormal values will be provided by subject number.

4.8.5 12-Lead ECG

For parameters of 12-lead ECG, measured values and changes from baseline will be summarized descriptively on scheduled time point, minimum post-baseline value and maximum post-baseline value.

ECG interpretation will be summarized with shift table from baseline to post-baseline timepoint and from baseline to worst post-baseline assessment with respect to clinical classification (Normal, Abnormal, NCS, Abnormal, CS).

Refer to the following definitions for summary of abnormal QTcF intervals:

Absolute values of QTcF intervals will be classified as:

- >450 msec to <=480 msec
- >480 msec to <=500 msec

- >500 msec

Changes of QTcF intervals from baseline will be classified as:

- Prolongation <= 30 msec
- Prolongation > 30 msec to <= 60 msec
- Prolongation > 60 msec

A listing of all ECG parameter will be provided by subject number.

4.8.6 Physical Examination

Physical examination results will not be summarized. A listing of all physical examination results will be provided by subject number.

4.8.7 Injection Site Reaction Assessment

The number, incidence of subjects with any injection site reaction will be summarized through the study. The incidence of each type (Pain, Tenderness, Erythema/Redness, and Induration/Swelling) and it's severity of injection site reaction will also be tabulated.

A listing of injection site reaction assessment will be provided by subject number.

4.8.8 Hospitalization Information

Hospitalization information will not be summarized. A listing of all hospitalization information will be provided by subject number.

4.8.9 Conjunctivitis Assessment

Treatment-emergent conjunctivitis is defined as conjunctivitis that started or worsened in severity on or after the first dose of study drug.

Treatment-emergent conjunctivitis will be summarized by worst post-baseline severity score.

A listing of conjunctivitis assessment will be provided by subject number.

4.9 Immunogenicity Analysis

The titers of anti-drug antibodies (ADA)-positive subjects will be listed, and the number, incidence of subjects with treatment emergent ADA after administration of BSI-045B will be described by blood sampling time points. The time to onset, titer, and duration of the presence of ADAs will be described using the mean, SD, median, quartiles, minimum, and maximum.

A listing of immunogenicity assessment will be provided by subject number.

4.10 Pharmacokinetics Analysis

For BLQ (below the lower limit of quantification) data before first dose, it will be analyzed as “0”. Concentrations of BSI-045B in serum will be summarized by time point using descriptive statistics.

A listing of pharmacokinetics assessment will be provided by subject number.

Other detailed PK analyses, including the derivation of PK parameters, will be provided in the PK Analysis Plan.

4.11 Pharmacodynamics/biomarker Analysis

For all pharmacodynamic/biomarkers evaluated in the present study, including serum levels of CCL17, periostin, total serum IgE, and perioheral eosinophil count will be statistically analyzed. The baseline for pharmacodynamics/biomarker parameter is defined as the last non-missing measured value prior to or on Day 1.

For BLQ (below the lower limit of quantification) data, it will be analyzed as “1/2 LLOQ”. For > ULOQ data, it will be analyzed as “ULOQ”. For all parameters, raw data, absolute and percent changes from baseline will be summarized by time point using descriptive statistics.

Mean (± standard deviation) of percent change from baseline will be plotted at scheduled visit.

Appendix 1. Imputation of Partial and Missing Dates

Incomplete Dates of Adverse Event

All AE start dates must be entered on the eCRF. In the rare case that all or part of an AE start date is missing, but an AE end date is present and after the first dose date, then the AE start date will be imputed as follows for the purpose of determining treatment emergent flag only:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Set date to first dose date
year = year of first dose	Missing	Missing/Non-missing	Set month and day to those of first dose
year ≠ year of first dose	Missing	Missing/Non-missing	Set month and day to January 1st
year = year of first dose	month = month of the first dose	Missing	Set day to the day of first dose
Non-missing	month ≠ month of the first dose	Missing	Set day to first day of onset month
year ≠ year of first dose	Non-missing	Missing	Set day to first day of onset month

If AE is not ongoing and AE end date is incomplete, AE end date will be imputed as follow:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.
- Completely missing dates will not be imputed.

The imputed AE end date will be compared with death date for subjects is known to be dead at the end of study or cut-off date, or last known alive date for subjects alive at the end of study or cut-off date. If it is later than the death date/last known alive date, the death date/last known alive date will be used to impute the incomplete date.

Incomplete Dates of Concomitant Drug/Non-Drug Treatment

- If year and month are present and day is missing, then set day to first day of month for start date and set day to last day of month for end date.
- If year and day are present and month is missing, then set month to January for start date and set month to December for end date.
- If year is present and month and day are missing, then set month and day to January 1st for start date and set month and day to December 31th for end date.
- If the imputed end date is later than death date or last known alive date at the end of study or cutoff date, then set it to the earlier date of death date or last known alive date at the end of study and cutoff date.
- Completely missing dates will not be imputed.
- If start date is completely missing and end date is on or after the first dose, then the treatment will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Treatment for which the start and end dates are completely missing will be classified as concomitant.

Incomplete Dates of Birth Date

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.
- Completely missing dates will not be imputed.

Incomplete Dates of AD Diagnosis

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.

The imputed date will be compared to first dose date. If it is later than the first dose date, the first dose date will be used to impute the incomplete date.

Appendix 1. Imputation of Partial and Missing Dates

Incomplete Dates of Adverse Event

All AE start dates must be entered on the eCRF. In the rare case that all or part of an AE start date is missing, but an AE end date is present and after the first dose date, then the AE start date will be imputed as follows for the purpose of determining treatment emergent flag only:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Set date to first dose date
year = year of first dose	Missing	Missing/Non-missing	Set month and day to those of first dose
year ≠ year of first dose	Missing	Missing/Non-missing	Set month and day to January 1st
year = year of first dose	month = month of the first dose	Missing	Set day to the day of first dose
Non-missing	month ≠ month of the first dose	Missing	Set day to first day of onset month
year ≠ year of first dose	Non-missing	Missing	Set day to first day of onset month

If AE is not ongoing and AE end date is incomplete, AE end date will be imputed as follow:

- If both the year and the month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31st of the year.
- Completely missing dates will not be imputed.

The imputed AE end date will be compared with death date for subjects is known to be dead at the end of study or cut-off date, or last known alive date for subjects alive at the end of study or cut-off date. If it is later than the death date/last known alive date, the death date/last known alive date will be used to impute the incomplete date.

Incomplete Dates of Concomitant Drug/Non-Drug Treatment

- If year and month are present and day is missing, then set day to first day of month for start date and set day to last day of month for end date.
- If year and day are present and month is missing, then set month to January for start date and set month to December for end date.
- If year is present and month and day are missing, then set month and day to January 1st for start date and set month and day to December 31th for end date.
- If the imputed end date is later than death date or last known alive date at the end of study or cutoff date, then set it to the earlier date of death date or last known alive date at the end of study and cutoff date.
- Completely missing dates will not be imputed.
- If start date is completely missing and end date is on or after the first dose, then the treatment will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Treatment for which the start and end dates are completely missing will be classified as concomitant.

Incomplete Dates of Birth Date

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.
- Completely missing dates will not be imputed.

Incomplete Dates of AD Diagnosis

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.

The imputed date will be compared to first dose date. If it is later than the first dose date, the first dose date will be used to impute the incomplete date.