Protocol Number:	BSI-045B-002
Protocol Title:	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
Indication:	Atopic dermatitis
Phase:	2a
Investigational Product:	BSI-045B
Sponsor:	Biosion, Inc. 5th Floor, Building D 3-1 Zhongdan Unit South Longshan Road Jiangbei New District, Nanjing
Key Sponsor Contacts:	[redacted], Biosion, Inc. & President, Biosion USA, Inc. [redacted] [redacted]
Date and Version:	Version 4.0, 8 Jul 2024

Confidentiality Statement

SPONSOR'S AGREEMENT

I have read the protocol version 4.0 entitled "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" and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines and all locally applicable regulations.

[redacted]

[redacted] Biosion, Inc. & President,
Biosion USA, Inc.

7/8/2024

Date (DD Month YYYY)

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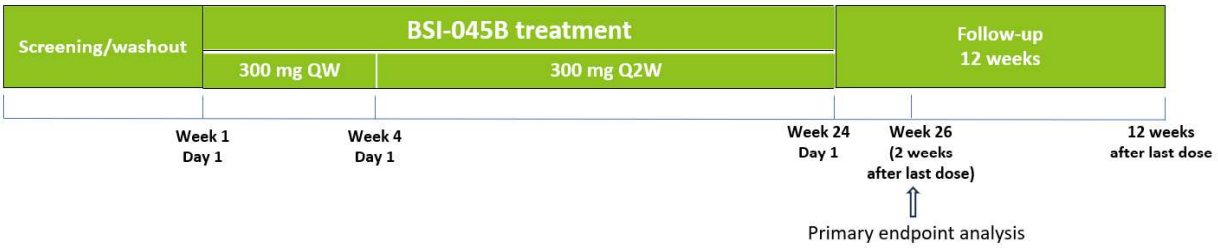
1 SCHEMA

BSI-045B-002 Study Design



2 PROTOCOL SYNOPSIS

Protocol No.	BSI-045B-002
Title	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
Version No. and Date	V 4.0, 8 Jul 2024
Sponsor	Biosion, Inc
Clinical Phase	2a
Study Drug	**Investigational Product** BSI-045B, anti-thymic stromal lymphopoietin (TSLP) mAb injection
Objectives	**Primary Objectives** ➢ To evaluate the efficacy of BSI-045B as monotherapy in patients with moderate to severe atopic dermatitis (AD) ➢ To evaluate the safety and tolerability of BSI-045B as monotherapy in patients with moderate to severe AD **Secondary Objectives** ➢ To evaluate the pharmacokinetics (PK) of BSI-045B ➢ To evaluate the immunogenicity of BSI-045B **Exploratory Objectives** ➢ To assess additional efficacy and safety outcomes of BSI-045B as monotherapy ➢ To evaluate the pharmacodynamic (PD) biomarkers of BSI-045B
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. 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.
Methodology	This study is a Phase 2a, proof-of-concept clinical study designed to evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD of BSI-045B injection, in patients with moderate to severe AD. The study will be unblinded. BSI-045B treatment will be initiated with a loading dose of 300 mg SC QW for 4 weeks. After that, patients will be treated Q2W to Week 24. After treatment, there will be a 12-week Follow-up Period. The preferred SC injection site is the abdomen. The thigh can be used as an alternative site for SC injections. A 2.5-mL injection of 120 mg/mL (300 mg total dose) will be administered at a single injection site. After injections, all patients should be monitored at the study sites for at least 30 mins to observe body reactions, including injection site reactions. Any injection site reactions observed after each site visit should be reported to the Investigators by the patients. The total number of evaluable patients with AD of the study is approximately 20 to 24, patients who do not complete the first 5 doses will be replaced. The SSC will monitor the study to identify questions concerning safety. The primary efficacy endpoint is the proportion of patients with ≥EASI75 at Week 26 (2 weeks after last dose at Week 24), compared with baseline (Day 1). Additional efficacy outcomes also include other scores on EASI, Investigator's Global Assessment (IGA), Facial IGA, and Peak Pruritus Numerical Rating Scale (PP-NRS). Efficacy assessments will be conducted at Screening, within the first hour prior to dosing on Day 1, at all subsequent visits, and at the time of early withdrawal from the study. Adverse events (AEs) will be collected after signing the Informed Consent Form (ICF) and throughout the Treatment Period and the Follow-Up Period. After injections, all patients should be monitored at the study sites for at least 30 mins to observe body reactions, including injection site reactions. Any injection site reactions observed after each site visit should be reported to the Investigators by the patients. Concomitant medications will be recorded after signing the ICF and throughout the Treatment Period and Follow-Up Period. No rescue medications will be allowed in this study.

	During the Treatment and Follow-up Periods, PK, PD, and immunogenicity samples will be collected for analysis. Follow-up assessments will occur during subsequent visits to the study sites. At the Investigator's discretion, patients may return to the study sites at other times for re-evaluation.
Number of evaluable Patients	Approximately 20 to 24 evaluable patients
Inclusion Criteria	Patients must meet the following criteria for study entry: 1) In the opinion of the Investigator, the patient is capable of understanding and complying with this protocol requirements. 2) The patient signs and dates a written ICF prior to the initiation of any study procedures. 3) The patient has a diagnosis of AD (according to the criteria established by Hanifin and Rajka, 1980). The diagnosis of AD must have been present for at least 6 months. 4) The patient is aged 18 to 65 years, inclusive at the time of consent. Patients of any gender are eligible. 5) A female patient weighs at least 45 kg and a male patient weighs at least 50 kg. The patient has a body mass index (BMI) between 18.0 and 32.0 kg/m^2 inclusive at Screening. 6) The EASI is ≥12 at Screening and on Day 1. 7) The score on the IGA is ≥3 (scale of 0 to 4) at Screening and on Day 1. 8) The total body surface area (BSA) affected by AD is ≥10% as assessed by the physical examination at Screening and on Day 1. 9) The patient has: (a) not received prior treatment with topical or systemic medications OR (b) the patient has active disease despite topical or systemic treatment as per the Investigator at the time of screening Prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products can be allowed if the patient agrees to continue using at the current dose during the study. 10) A male patient who is non-sterilized and sexually active with a female partner of childbearing potential agrees to use highly effective contraception from the time of signing the ICF throughout the duration of the study treatment and for 90 days (~5 half-lives) after the last dose of study drug (See Section 8.3). 11) A female patient of childbearing potential who is sexually active with a non-sterilized male partner agrees to routinely use highly effective contraception from the time of signing the ICF throughout the duration of the study treatment and for 90 days after the last dose of study drug (See Section 8.3).

<table>
<tr><td></td><td>12) The patient has a negative urine/blood result for drugs of abuse (if there are concerns in the opinion of the Investigator regarding the use of illicit drugs, including cannabinoid products) at Screening.</td></tr>
<tr><td>Exclusion Criteria</td><td>Any patient who meets any of the following criteria will be excluded from the study:

1) The patient has received any of the following treatments but did not finish the required washout as stated in the following table. After the washout period, the patients can be considered for study treatment.

<table>
<tr><th>Therapy</th><th>Washout Duration Required before First Dose of BSI-045B</th></tr>
<tr><td>Tralokinumab</td><td>12 weeks</td></tr>
<tr><td>Dupilumab</td><td>12 weeks</td></tr>
<tr><td>Phototherapy</td><td>4 weeks</td></tr>
<tr><td>Abrocitinib</td><td>4 weeks</td></tr>
<tr><td>Upadacitinib</td><td>4 weeks</td></tr>
<tr><td>Topical corticosteroids</td><td>1 week</td></tr>
<tr><td>Topical calcineurin inhibitors</td><td>1 week</td></tr>
<tr><td>Investigational Products</td><td>4 weeks</td></tr>
<tr><td>All Other Therapies prescribed for therapeutic immunosuppression or immunomodulation</td><td>3 weeks or 4 half-lives, whichever is longer</td></tr>
</table>
2) The patient has another dermatologic condition that might confound a diagnosis of AD or a treatment assessment.

3) The patient has any clinically significant illness that may affect the safety, increase the risk for seizure or lower the seizure threshold, or potentially confound the study results, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality. It is the responsibility of the Investigator to assess the clinical significance of a patient's condition; however, consultation with the Sponsor's Medical Monitor may be warranted.

4) The patient has abnormal laboratory values during the Screening Period: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 1.5 times the upper limit of normal (ULN), total bilirubin ≥ 1.5 mg/dL, estimated glomerular filtration rate (GFR) < 60 mL/min (based on Cockcroft-Gault calculation), hemoglobin (Hgb) ≤ 10 g/dL, platelet count ≤ 150 $\times 10^3/\mu L$. Individual exceptions may be granted with the agreement of the Sponsor and the Investigator.

5) The patient has a history of anaphylaxis following biologic therapy.

6) The patient has a history of allergy to corticosteroids, diphenhydramine, hydroxyzine, cetirizine, or fexofenadine.

7) The patient has a history of a clinically significant infection within 4 weeks prior to Screening.

8) The patient has been diagnosed with a helminthic parasitic infection within 6 months prior to Screening.

9) The patient has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening or is unwilling to agree to abstain from excessive alcohol consumption and drugs (including cannabinoids) throughout the study.</td></tr>
</table>

	10) The patient had a major surgical or major dental procedure within 8 weeks prior to Screening. 11) The patient is pregnant or lactating or intends to donate ova before, during, or within 90 days (~ 5 half-lives) since the last dose of study drug. 12) If male, the patient intends to donate sperm during this study or within 90 days (~ 5 half-lives) since the last dose of study drug. 13) The patient has a history of neurologic abnormalities including abnormal electroencephalography, brain injury including traumatic injury, perinatal cerebropathy, postnatal brain damage, blood-brain barrier abnormality, and cavernous angioma. 14) The patient has a history of cerebral arteriosclerosis. 15) The patient has a history of cancer, except for adequately treated basal or squamous cell skin cancer or in situ cancers; or any other cancer from which the patient has been disease free for at least 5 years prior to the first dose of study drug. 16) The patient has a positive test result for hepatitis B surface antigen (HbsAg), antihepatitis C virus (HCV), a history of active tuberculosis, a positive test result for human immunodeficiency virus (HIV), or a known history of HIV infection at Screening. 17) The patient has poor peripheral venous access. 18) The patient has donated or lost ≥ 450 mL of blood (including plasmapheresis) or had a transfusion of any blood product within 90 days prior to the first dose of study drug. 19) The patient has an abnormal (clinically significant) electrocardiogram (ECG) at Screening and/or on Day 1. Entry of any patient with an abnormal (not clinically significant) ECG must be approved and documented by signature of the Investigator. In the case of a corrected QT interval (Fridericia) (QTcF) > 450 ms or > 470 ms (patients with bundle branch block) or PR interval outside the range of 115 to 220 ms, assessment may be repeated once for eligibility determination at Screening and/or on Day 1. 20) The patient has poorly controlled hypertension and is not considered suitable for participation in this study in the judgement of the Investigators at Screening and/or on Day 1. 21) The patient has abnormal resting heart rate and is not considered suitable for participation in this study in the judgement of the Investigator at Screening and/or on Day1. Assessment is allowed to be repeated once for eligibility determination at Screening and/or on Day 1 if deemed necessary. 22) The patient plans to use any other prohibited medication or undergo any prohibited procedure during the study. Oral antibiotics are permitted. Bleach baths are not permitted. 23) The patient has a risk of suicide on the Patient Health Questionnaire-2 (PH-2) or in the judgment of the Investigator, or the patient has made a suicide attempt or has a history of deliberate self-harm within 6 months prior to Screening. 24) The patient is compulsorily detained for a medical or psychiatric illness.

	25) The patient or their immediate family are personnel at the study site. 26) The patient is unable to comply with restrictions and prohibited activities/treatments as listed in the study protocol.
Study Endpoints	**Primary Efficacy Endpoint:** Proportion of patients with ≥EASI75 at Week 26 (2 weeks after last dose at Week 24) **Primary Safety Endpoint:** Safety and tolerability as evidenced by the incidence of AEs, anti-BSI-045B antidrug antibody (ADA) formation, clinical laboratory evaluations, 12-lead ECGs, vital signs, physical examinations. The relationships between study drugs and AEs will be evaluated by Investigators. **Secondary Endpoints**: Pharmacokinetics listings will be provided. PK parameters might be estimated through compartmental modeling. Additionally, the PK/Efficacy relationship might be explored. *Immunogenicity*: Anti-BSI-045B ADA during and post BSI-045B treatment. *PD biomarkers*: Serum levels of thymus and activation related chemokine/C-C chemokine ligand 17 [TARC/CCL-17], periostin, and IgE during and post BSI-045B treatment. **Exploratory Endpoints:** • 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 IGA 0 or 1 at Week 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
Stopping Criteria	If a patient experiences an AE assessed as ≥ Grade 3 (≥ Grade 2 for the system-organ class of Cardiac Disorders) according to Common Terminology Criteria for Adverse Events (CTCAE v5), then: 1) BSI-045B treatment may be continued if the AE is considered to be unrelated to BSI-045B; 2) BSI-045B treatment will be withheld if the AE is considered to be related to BSI-045B, until the toxicity returns to ≤ Grade 2; 3) BSI-045B will be permanently discontinued if the AE recurs to ≥ Grade 3 after BSI-045B treatment resumed and is considered to be BSI-045B related. Treatment discontinuation decisions will be made by Investigators after a discussion with Sponsor. These AEs include hepatotoxicity, injection site reactions, allergic conjunctivitis and hypersensitivity (see Table 8).

	Patients who experience such AEs will be followed until the adverse events resolves or stabilizes. Study drug administration will not be discontinued. If 2/3 of patients experience any adverse event assessed as ≥ Grade 3 (≥ Grade 2 for the system-organ classes of Cardiac Disorders) per CTCAE v5, the study should be suspended for an evaluation from SSC.
Screening Assessments	Screening assessments will be performed after the patients signed the ICF. After all screening results are obtained, eligible patients who require no washout will be enrolled to the study directly; eligible patients who require washout will start washout and repeat some screening assessments during Day -14 to Day -1. A complete history will be recorded at Screening and will include medical history, surgical history, smoking history, alcohol use history, drug abuse history, prior and current medication, blood donation history, allergy history, and other demographic information. Physical examinations at Screening will include weight, height, BMI, as well as a complete examination. Symptom-driven examinations will be performed at other time points. Other screening assessments will include 12-lead ECG, blood pregnancy test (females of childbearing potential only), and vital signs (blood pressure, pulse, temperature, and respiratory rate). A subset of these tests will be completed at other time points, as detailed in the Schedule of Activities. A screening for drugs of abuse is optional (per the discretion of the Investigator). Clinical laboratory assessments at Screening will include the following: - *Hematology*: Hgb, hematocrit, white blood cell (WBC) count and differential, red blood cell (RBC) count and indices, platelet count - *Chemistry*: Sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, glucose, BUN, creatinine, uric acid, ALT, AST, gamma glutamyl transferase (GGT), alkaline phosphatase, total protein, albumin, globulin, total bilirubin, lactate dehydrogenase (LDH), total cholesterol, triglycerides - *Coagulation:* Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, international normalized ratio (INR) - *Virology (performed only at Screening):* HbsAg, anti-HCV, HIV - *Urinalysis*: Protein, glucose, ketones, occult blood, urobilinogen, urine sediment microscopy (if other parameters abnormal)
Efficacy Assessments	Patients will be assessed to determine an EASI score at Screening, within the first hour prior to dosing on Day 1 (baseline), at subsequent visits, and at the time of early withdrawal from the study. 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 (Hanifin and Rajka, 1980). The primary efficacy endpoint is the proportion of patients with ≥EASI75 at Week 26 (2 weeks after last dose at Week 24).

	The IGA and facial IGA requires the Investigator to rate the severity of AD on a scale from 0 (clear) to 4 (severe). Assessments will be made on Day 1 and at subsequent visits, and at the time of early withdrawal from the study. The assessment tool for itching is the PP-NRS, on which the patient 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. Patients will complete the rating scale daily using the patient diary beginning on Day -8, throughout the last study visit, and at the time of early withdrawal from the study. In order to calculate an average for the score, the patient must have completed the diary for a minimum of 4 days during the previous 7 days. At each visit, the percentage of patients who achieve 50%, 75%, and 90% improvement in the EASI score from Day 1 and the change in EASI score from Day 1 will be calculated. Detailed assessment of additional exploratory efficacy endpoints is described in the Statistical Analysis Plan (SAP).
Safety Assessments	The safety of BSI-045B will be assessed by the incidence of AEs, anti-BSI-045B antibody formation, clinical laboratory evaluations, 12-lead ECGs, vital signs, and physical examinations, as well as occurrence of conjunctivitis. The relationships between study medication and AEs will be evaluated by the Investigators.
Pharmacokinetic Assessments	Serial blood samples (4 mL) for PK assessments will be collected at the following time points relative to the SC injection of BSI-045B: within 1 h before each dose during the Treatment Period, on each visit during the Follow-up Period, and at the time of early withdrawal from the study drug.
Immunogenicity	Blood samples (4 mL) will be drawn from patients to determine anti-BSI-045B ADA status (negative or positive with titer). Blood samples will be collected at the following time points relative to SC injection of BSI-045B: W1D1, W2, W3, W4, W8, W12, W16, W20, and W24 within 1 h before dose during the Treatment Period, at FU2, FU4, and FU6 during the Follow-up Period, and at the time of early withdrawal from the study drug.
Pharmacodynamic / Biomarker Assessments	Blood samples (4 mL) for serum TARC/CCL 17, periostin, and IgE concentrations will be collected at W1D1, W2, W3, W4, W8, W12, W16, W20, and W24 within 1h before dose during the Treatment Period, at FU2, FU4, and FU6 during the Follow-up Period, and at the time of early withdrawal from the study drug.
Enrollment, Randomization, and Blinding	The study will not be randomized and will be unblinded.
Statistical Methods	**Sample size calculations:** 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%. **Statistical approach:** Statistical analyses will be descriptive in nature, with frequencies and percentages generated for categorical variables and mean, standard deviation,

	median, minimum, and maximum values generated for continuous variables. Exact one-sided 95% confidence intervals will be generated for primary and select secondary efficacy endpoints based on proportions. Additional details regarding the statistical analyses will be presented in the SAP.
Sample Handling	Samples for serum PK, ADA, and biomarker assessments will be collected for PK and ADA assessments using Good Laboratory Practice (GLP)-validated assays and for PD biomarker assessments using fit-for-purpose qualified assays with commercial kits. Refer to the laboratory manual for additional details on laboratory assessment and sample processing.

3 SCHEDULE OF ACTIVITIES

The Schedule of Activities is divided into two tables:

Table 1. Screening and Treatment

Table 2. Follow-up, End of Study, and Early Withdrawal

Table 1. Screening and Treatment

Study Procedure	Screening [1]	Treatment Period															
		QW Loading Dose					W4 (±3d)	W6 (±3d)	W8 (±3d)	W10 (±3d)	W12 (±3d)	W14 (±3d)	W16 (±3d)	W18 (±3d)	W20 (±3d)	W22 (±3d)	W24 (±3d)
		W1 D1		W1 D2	W2 (±1d)	W3 (±1d)											
		Predosing[2]	Dosing and after														
Sign ICF	X																
Inclusion/exclusion criteria	X	X															
Medical history, demographics	X																
Assessment of suicidality (PH-2)	X																
AD medication washout	X																
BSI-045B administration			X		X	X	X[3]										
12-lead ECG[4]	X	X		X	X		X		X		X			X		X	X
Vital signs[4]	X	X		X	X		X		X		X		X		X		X
Physical examination[5]	X	X		X	X		X		X		X		X		X		X
Clinical labs[4,6]	X[7]	X			X		X		X		X		X		X		X
Blood pregnancy test (females of childbearing potential only)	X																
Urine pregnancy testing (females of childbearing potential only)		X					X		X		X		X		X		X
Urine toxicology for drugs of abuse (optional)[8]	X[7]																
Virology screen[4,8]	X																
Assess for injection site reaction [10]			X	X	X												

Study Procedure	Screening [1]	Treatment Period															
		QW Loading Dose					W4 (±3d)	W6 (±3d)	W8 (±3d)	W10 (±3d)	W12 (±3d)	W14 (±3d)	W16 (±3d)	W18 (±3d)	W20 (±3d)	W22 (±3d)	W24 (±3d)
		W1 D1		W1 D2	W2 (±1d)	W3 (±1d)											
		Predosing[2]	Dosing and after														
Efficacy and safety assessments and patient diary (EASI, IGA, facial IGA, PP-NRS, assessment of conjunctivitis)[11]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample collection[4,11]		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity sample collection[4,13]		X			X	X	X		X		X		X		X		X
PD Biomarker sample collection[4,14]		X			X	X	X		X		X		X		X		X
Assess concomitant medications	X																
Monitor and document AEs	X																

AD = atopic dermatitis; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CCL-17 = C-C chemokine ligand 17; D = day; EASI = Eczema and Severity Index; ECG = electrocardiography; GGT = gamma glutamyl transferase; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = Informed Consent Form; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IL = interleukin; INR = international normalized ratio; LDH = lactate dehydrogenase; PD = pharmacodynamic; PH-2 = Patient Health Questionnaire-2; PK = pharmacokinetic; PP-NRS = Peak Pruritus Numerical Rating Scale; PT = prothrombin time; Q2W = every 2 weeks; QW = every week; RBC = red blood cell; SC = subcutaneous; TARC = thymus and activation regulated chemokine; W = week; WBC = white blood cell.

1. Screening duration varies by prior AD treatment and the Investigator should consult Section 7.2 for required washout duration.
For patients not requiring washout, screening assessments should be conducted after ICF been signed and the screening period will take up to 2 weeks; once they complete their screening assessments and meet all study inclusions/exclusions, the patients will advance directly to W1D1.
For patients requiring washout, screening assessments should be conducted after ICF been signed, if all inclusion/exclusions are met, they will be notified by the study sites to start the washout for prior AD treatment. Screening assessments should be repeated if they are performed ≥14 days before W1D1.
2. W1D1 pre-dosing is set to confirm the eligibility of patients.
3. BSI-045B administration after W4 (4 loading doses) at Q2W interval to Week 24.

4. Order of assessments: When collecting PK, immunogenicity, biomarker, and clinical laboratory samples, vital signs, and/or ECG assessments are scheduled to occur at the same time point, ECG and vital signs testing will be performed prior to blood collections. The preferred order of assessments is: 1) ECG, 2) vital signs, 3) PK, immunogenicity, and biomarker sampling, 4) clinical laboratory sampling.
5. Height and weight, and BSA affected by AD should be determined at the Screening physical examination. BSA affected by AD should also be determined at W1D1 pre-dosing. Symptom-driven examinations will be performed at other time points beyond screening.
6. Clinical laboratory assessments:

- *Hematology*: Hemoglobin, hematocrit, WBC count and differential, RBC count and indices, platelet count
- *Chemistry*: Sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, glucose, BUN, creatinine, uric acid, ALT, AST, GGT, alkaline phosphatase, total protein, albumin, globulin, total bilirubin, LDH, total cholesterol, triglycerides
- *Coagulation*: PT, aPTT, fibrinogen, INR
- *Urinalysis*: Protein, glucose, ketones, occult blood, urobilinogen, urine sediment microscopy (if other parameters abnormal)

7. For patients requiring washout, clinical laboratory assessments and urine toxicology test should be repeated to make sure the tests are conducted within 14 days prior to W1D1.
8. Urine toxicology: Urine toxicology testing is optional. If the PI has no concerns about the use of illicit drugs by a patient, testing for drugs of abuse is not required. If the PI has concerns, a negative urine/blood result for drugs of abuse is required at Screening. Screening assessment on urine toxicology should be repeated if they are performed ≥14 days before W1D1.
9. Virology screening: HbsAg, anti-HCV, HIV.
10. All patients should be monitored in the study sites for at least 30 mins after each dose to observe body reactions, including injection site reactions. Any injection site reactions observed after each site visit should be reported to the Investigators by the patients.
11. Efficacy assessments: EASI, IGA, facial IGA and PP-NRS. For PP-NRS: Patients will complete the PP-NRS daily in a patient diary beginning on Day -8, throughout the last study visit, and at the time of early withdrawal from the study, and scores for each timepoint will be the average of scores over the past 7 days. In order to calculate an average for the score, the patient must have completed the diary for a minimum of 4 days during the previous 7 days. Investigator should also assess Facial IGA. For the assessment of conjunctivitis, diagnosis history with severity will be recorded at screening, and at every visit during the treatment period, all patients will be asked if they had been diagnosed as conjunctivitis since last visit. Conjunctivitis severity grade includes: 0 = no conjunctivitis; 1 = mild conjunctivitis; 2 = moderate conjunctivitis requiring treatment; 3 = severe conjunctivitis that may require an ophthalmic exam. Investigators should also check the patients' eyes and record any findings.
12. PK blood sample collection: Within 1 h before each dose during the Treatment Period.
13. Immunogenicity blood sampling: Blood samples are to be collected at W1D1, W2, W3, W4, W8, W12, W16, W20, and W24 within 1 h before each dose during the Treatment Period.
14. Biomarker blood sample collection: Assessments are TARC/CCL-17, periostin, and IgE. Samples are to be obtained at W1D1, W2, W3, W4, W8, W12, W16, W20, and W24 within 1 h before each dose during the Treatment Period.

Table 2. Follow-up, End of Study, and Early Withdrawal

Study Procedure	Follow-up Period						Early Withdrawal[1]
	FU1 (2 weeks after last dose±3d)	FU2 (4 weeks after last dose±3d)	FU3 (6 weeks after last dose±3d)	FU4 (8 weeks after last dose±3d)	FU5 (10 weeks after last dose±3d)	FU6 (12 weeks after last dose±3d)	(+7d)
12-lead ECG[2]	X						X
Vital signs[2]	X	X	X	X	X	X	X
Physical examination (system driven)		X		X		X	X
Clinical labs[2,3]		X		X		X	X
Blood pregnancy test (females of childbearing potential only)							X
Urine pregnancy testing (females of childbearing potential only)		X		X		X	
Efficacy assessments and patient diary (EASI, IGA, facial IGA, PP-NRS)[4]	X	X	X	X	X	X	X
PK sample collection[2,5]	X	X	X	X	X	X	X
Immunogenicity sample collection[2,6]		X		X		X	X
PD Biomarker sample collection[2,7]		X		X		X	X
Assess concomitant medications	X						
Monitor and document AEs	X						

AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CCL-17 = C-C chemokine ligand 17; EASI = Eczema and Severity Index; ECG = electrocardiography; GGT = gamma glutamyl transferase; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IL = interleukin; INR = international normalized ratio; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; PP-NRS = Peak Pruritus Numerical Rating Scale; PT = prothrombin time; RBC = red blood cell; TARC = thymus and activation regulated chemokine; W = week; WBC = white blood cell

1. Early withdrawal: Early withdrawal assessments must be completed within 7 days after the last treatment with BSI-045B or within 7 days after the patient's decision to discontinue study treatment, whichever occurs first. When medically feasible, the Medical Monitor should be consulted prior to study drug discontinuation.
2. Order of assessments: When collecting PK, immunogenicity, biomarker, and clinical laboratory samples, vital signs, and/or ECG assessments are scheduled to occur at the same time point, ECG and vital signs testing will be performed prior to blood collections. The preferred order of assessments is: 1) ECG, 2) vital signs, 3) PK, immunogenicity, and PD/biomarker sampling, 4) clinical laboratory sampling.

3. Clinical laboratory assessments:
   - *Hematology*: Hemoglobin, hematocrit, WBC count and differential, RBC count and indices, platelet count
   - *Chemistry:* Sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, glucose, BUN, creatinine, uric acid, ALT, AST, GGT, alkaline phosphatase, total protein, albumin, globulin, total bilirubin, LDH, total cholesterol, triglycerides, CK, CK isoenzymes
   - *Coagulation:* PT, aPTT, fibrinogen, INR
   - *Urinalysis:* Protein, glucose, ketones, occult blood, urobilinogen, urine sediment microscopy (if other parameters abnormal)
4. Efficacy assessments: EASI, IGA, facial IGA, and PP-NRS. Patients will complete the PP-NRS daily throughout the last study visit, and at the time of early withdrawal from the study, and scores for each timepoint will be the average of scores over the past 7 days. In order to calculate an average for the score, the patient must have completed the diary for a minimum of 4 days during the previous 7 days. Investigator should also assess Facial IGA.
5. PK blood sample collection: At each visit during the Follow-up Period, and at the time of early withdrawal from the study drug.
6. Immunogenicity blood sampling: Blood samples are to be collected at FU2, FU4, and FU6 during the Follow-up Period, and at the time of early withdrawal from the study drug.
7. Biomarker blood sample collection: Assessments are TARC/CCL-17, periostin, and IgE. Samples are to be obtained at FU2, FU4, and FU6 during the Follow-up Period, and at the time of early withdrawal from the study drug.

4 LIST OF ABBREVIATION

Abbreviation	Definition
AD	atopic dermatitis
ADA	antidrug antibody
ADL	activity of daily living
AE	adverse event
ALT	alanine aminotransferase
AMIT	Acumen Medical Information & Technology Co., Ltd.
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-7}	area under the serum drug concentration-time curve from time 0 to 7 days
AUC_{inf}	area under the serum drug concentration-time curve from last dose extrapolated to infinity
AUC_{last}	area under the serum drug concentration-time curve from last dose to the last quantifiable drug concentration
AUCτ	area under the serum drug concentration-time curve
BMI	body mass index
BSA	body surface area
CCL-17	C-C chemokine ligand 17
CI	confidence interval
C_{ave}	average serum drug concentration
C_{min}	minimum observed serum drug concentration
C_{max}	maximum observed serum drug concentration
CRF	Case Report Form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTTQ	ChiaTai Tianqing Pharmaceutical Group Co., Ltd
D	day
EASI	Eczema Area and Severity Index
ECG	electrocardiography
EOS	end of study
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
Hgb	hemoglobin
HIV	human immunodeficiency virus
HV	healthy volunteer
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	interleukin
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	multiple ascending dose
NOAEL	no observed adverse effect level
NRS	Numerical Rating Scale
PCR	polymerase chain reaction
PD	pharmacodynamic
PH-2	Patient Health Questionnaire-2
PI	Principal Investigator
PK	pharmacokinetic
PP-NRS	Peak Pruritus Numerical Rating Scale
PT	prothrombin time
Q2W	every other week
Q7D	every 7 days (weekly)

QTcF	corrected QT interval, Fridericia
QW	every week
R_{auc}	ratio of AUCτ at last dose / AUC_{0-7}
RBC	red blood cell
RC_{max}	ratio of C_{max} at last dose / C_{max}
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SSC	Safety Steering Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal elimination half-life
TARC	thymus and activation regulated chemokine
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
Th2	helper T cell 2
T_{max}	time to maximum serum drug concentration
TRPA1	transient receptor potential ankyrin 1
$T_{ss,max}$	time to maximum serum drug concentration at steady state
TSLP	thymic stromal lymphopoietin
TSLPR	thymic stromal lymphopoietin receptor
ULN	upper limit of normal
W	week
WBC	white blood cell

5 INTRODUCTION AND BACKGROUND

5.1 Disease Overview

Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease and is the most common type of eczema, affecting more than 9.6 million children and about 16.5 million adults in the United States. Worldwide prevalence ranges from 0.2% to 24.6%, with the highest rates of AD seen in children in Africa and Latin America (Odhiambo et al, 2009). Atopic dermatitis is a chronic relapsing and remitting condition that may overlap with other types of eczema and may progress through a process called atopic march to food allergies, asthma (up to 70%), and rhinitis (He and Geha, 2010; Locksley et al, 2010). Thymic stromal lymphopoietin (TSLP) plays a key role in the triad of atopic diseases: asthma, allergic rhinitis, and AD (Ziegler et al, 2013).

5.2 Development of BSI-045B

5.2.1 Mechanism of Action

BSI-045B (the investigational product [IP]) is a humanized IgG1 subtype mAb that targets TSLP. It is being co-developed by ChiaTai Tianqing Pharmaceutical Group Co., Ltd (CTTQ) and Biosion, Inc., China.

TSLP protein is one of the key molecules that mediate allergic reactions. The TSLP protein belongs to the interleukin-2 (IL-2) cytokine family, which has actions similar to IL-7. TSLP is mainly derived from the barrier surface of epithelial cells in skin, intestine, and lung tissues, and responds to danger signals by regulating type 2 inflammatory responses at mucosal barriers in allergic inflammation (Han et al, 2020). The protein acts on a variety of immune cells (eg, dendritic cells) by forming complexes with the TSLP receptor (TSLPR) and IL-7 receptor on the cell surface to drive downstream helper T cell 2 (Th2) cytokine release. It also activates cells involved in non-Th2-driven inflammation and promotes the expression of inflammatory cytokines such as IL-4, IL-5, and IL-13. Abnormally high TSLP protein expression is related to a variety of atopic diseases including asthma, AD, allergic rhinitis, eosinophilic esophagitis, cancer, arthritis, intestinal parasites, and other diseases (Nakajima et al, 2020).

BSI-045B specifically binds to human TSLP, blocking its interaction with the receptor complex and interrupting signal transduction, thereby preventing immune cells targeted by TSLP from releasing proinflammatory cytokines. BSI-045B has good in vitro binding affinity to HuTSLP (K_D(mol/L) <1.08E^{-12}) and to cynoTSLP (K_D (mol/L) <7.14E^{-13}), and has a higher affinity than tezepelumab (K_D(mol/L) =6±2E^{-11}) (Verstraete et al, 2017). In vivo efficacy of BSI-045B showed a significant dose-dependent therapeutic effect in a cynomolgus asthma model. Other studies determined that BSI-045B can significantly reduce the level of eosinophils in alveolar lavage fluid, reducing lung resistance and improving lung compliance. The effectiveness of BSI-045B in this model appeared equivalent to the reference drug tezepelumab at the same dose (BSI-045B Investigator's Brochure).

5.2.2 Preclinical Findings

In preclinical studies, BSI-045B exhibited good absorption characteristics after subcutaneous (SC) injection and exposure was proportional to the increase in dose. There was no difference between sexes in drug exposure (BSI-045B Investigator's Brochure).

5.2.3 Phase 1 Study (BSI-045B-001)

A Phase 1 study is being conducted by the Sponsor to evaluate the safety, tolerability, immunogenicity, pharmacokinetic (PK) profile, and activity of BSI-045B injection after single and multiple doses in adult healthy volunteers (HVs) and patients with AD.

5.2.3.1 Study Design

The Phase 1 study employs a randomized, double-blind, placebo-controlled design. The study consists of 3 parts: a single -ascending dose (SAD) study in HVs, a single-dose study in patients with AD, and a multiple -ascending dose study (MAD) study in HVs. The study is ongoing, and an interim analysis was conducted to analyze the safety and PK data. In this interim analysis, all subjects enrolled in Part A (SAD) and in the lowest dose level cohort (5 doses, 240 mg weekly [Q7D]) in Part C (MAD) had completed the study and data was analyzed up to end of study (EOS). Subjects enrolled in the second dose level cohort (3 doses, 480 mg Q7D) in Part C (MAD) had completed the study up to Day 84 (final dose administered on Day 15, EOS Day 104) and data was analyzed up to Day 84. Serum BSI-045B concentrations versus time data are available up to Day 56. All subjects enrolled in Part B (patients with AD) had completed the study up to Day 43 (single dose administered on Day 1, EOS Day 113) and data was analyzed up Day 43. Serum BSI-045B concentrations versus time data are available up to Day 15.

All study objectives and endpoints shown in Table 3 are as stated in the BSI-045B-001 study protocol version 4.0, dated 20 September 2022.

Table 3. Objectives and Endpoints, Phase 1 Study (BSI-045B-001)

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of BSI-045B	AEs, clinical laboratory assessments, vital signs, ECGs, physical examinations
Secondary	
To evaluate the pharmacokinetics (PK) of BSI-045B	Primary: C_{max}, T_{max}, $t_{1/2}$, AUC_{inf}, AUC_{last} (Other PK parameters may also be included)
To evaluate the activity of BSI-045B in patients with moderate to severe AD over one dosing interval	50% and 75% improvement from Day 1 in EASI scores Pruritus NRS (daily)

To evaluate the immunogenicity of BSI-045B	ADA at Day 1 and post BSI-045B treatment
To collect serum samples for possible future evaluation of PD biomarkers of BSI-045B target engagement	IL-4, IL-5, IL-13, IL-17, TARC/CCL-17, periostin, and IgE at Day 1 prior and post BSI- 045B treatment to be evaluated in patients with AD

ABBREVIATIONS: AD = atopic dermatitis; ADA = antidrug antibodies; AE = adverse event; AUC_{inf} = area under the serum drug concentration-time curve from last dose extrapolated to infinity; AUC_{last} = area under the serum drug concentration-time curve from time last dose to the last quantifiable drug concentration; CCL-17 = C-C chemokine ligand 17; C_{max} = maximum observed serum drug concentration; EASI = Eczema Area and Severity Index; ECG = electrocardiography; IgE = immunoglobulin E; IL = interleukin; NRS = Numerical Rating Scale; PD = pharmacodynamic; PK = pharmacokinetic; $t_{1/2}$ = apparent terminal elimination half-life; TARC = thymus and activation regulated chemokine; T_{max} = time to maximum serum drug concentration

In detail the 3 parts of the study are:

- Part A SAD cohorts: To evaluate the safety, tolerability, PK, and immunogenicity of single ascending doses of BSI-045B administered as an SC injection of 120, 240, 480, and 720 mg to HVs. Eight (8) (6 Active:2 Placebo) subjects were enrolled in each dose level cohort (total 32 subjects) as outlined in Table 4.
- Part B single dose cohort: To evaluate the safety, tolerability, PK, activity (as measured by the Eczema Area and Severity Index [EASI] score), and immunogenicity of a single dose of BSI-045B administered as a SC injection of 480 mg to patients with AD. A total of 12 subjects (9 Active:3 Placebo) were planned to be enrolled in the cohort as outlined in Table 4. However, due to difficulties in identifying and enrolling AD patients into Part B, a total of 5 AD patients (4 Active: 1 Placebo) are participating in this ongoing study.
- Part C MAD cohorts: To evaluate the safety, tolerability, PK, and immunogenicity of multiple ascending doses of BSI-045B administered as SC injections Q7D to HVs for 5 cycles at the 240 mg dose level and for 3 cycles at the 480 mg dose level. Eight (8) (6 Active:2 Placebo) subjects were planned for each dose level cohort. Due to one withdrawal in the 240 mg Q7D cohort, an additional subject was enrolled and treated with BSI-045B. A total of 17 subjects were enrolled (240 mg Q7D cohort: [7 BSI-045B:2 Placebo]; 480 mg Q7D cohort: [6 BSI-045B:2 Placebo]) as outlined in Table 4.

In total, 55 subjects (49 HVs, 5 patients with AD, and 1 withdrawal) were enrolled at the time of the interim analysis.

Table 4. Treatments Administered per Cohort in Study BSI-045B-001

Cohort Number	Dose Level (mg)	Total Number of Doses	# SC injections		Volume administered (mL)	Number of Participants		
			BSI-045B	Placebo		Randomized to BSI-045B	Randomized to Placebo	Total
Part A – SAD, HVs								
1	120	1	1	1	1	6	2	8
2	240	1	1	1	2	6	2	8
3	480	1	2	2	4	6	2	8
4	720	1	3	3	6	6	2	8
Part B – Single dose, patients with AD								
1	480	1	2	2	4	4	1	5
Part C – MAD, HVs								
1	240 Q7D	5	1	1	2	7[1]	2	9[1]
2	480 Q7D	3	2	2	4	6	2	8

1. One subject in Cohort C1 withdrew from the study after the first dose and was replaced.

AD = atopic dermatitis; HV = healthy volunteer; MAD = multiple ascending dose; Q7D = every 7 days; SAD = single ascending dose; SC = subcutaneous.

Part C of the study was originally planned to consist of 3 MAD cohorts: 240 mg, 480 mg, and 600 mg. In each cohort, subjects were to receive a total of 5 doses, administered once Q7D. Following a Safety Review Committee meeting conducted on 30 August 2022, during which the committee reviewed safety, tolerability, and PK data from the Part A cohorts and Part C first MAD cohort, a decision was made to reduce the dosing schedule for the second MAD cohort (480 mg dose level) from 5 cycles to 3 cycles and not conduct the third cohort (600 mg Q7D). The basis for this decision was the apparent accumulation of BSI-045B based on the mean maximum observed serum drug concentration (C_{max}). The mean C_{max} determined in the MAD Cohort 1 (240-mg dose level after 5 weekly SC injections) slightly exceeded the mean C_{max} determined from the 720-mg dose level in SAD Cohort 4.

5.2.3.2 Safety of BSI-045B

Per the interim report for this Phase 1 study, there were no serious treatment-emergent adverse events (TEAEs), TEAEs leading to death or any deaths in any part of the study. There was one (1; 12.5% of group) severe TEAE (transaminases increased), reported by a subject in the 240-mg dose level cohort in Part A. One (1; 11.1% of group) subject (Part C; 240-mg Q7D cohort) who experienced increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT) withdrew from the study.

Among HVs in the study, TEAEs were similarly frequent across all single and multiple dose levels, with most or all subjects in each cohort in Part A (SAD) and Part C (MAD) reporting at least one TEAE. In Part A, the frequency of study drug related TEAEs increased with dose level, indicating a potential relationship. In Part C, there was no increase in the frequency of study drug related TEAEs increasing with dose level.

Treatment-emergent AEs in system organ class (SOC) General Disorders and Administration Site Conditions, most or all of which were injection site reactions, were the most common TEAEs by SOC.

In the single-dose cohort (480 mg) in AD patients, no TEAE by Preferred Term was reported by greater than 1 (20.0%) of subjects. The frequency of TEAEs (2 [40.0%]) in the single dose- (480 mg) cohort in patients with AD was lower than the frequency of TEAEs (7 [87.5%]) in the 480 mg single-dose cohort in HVs.

No deaths or other serious adverse events (SAEs) were reported in the study.

5.2.3.3 Pharmacokinetics of BSI-045B

In addition to the safety and tolerability assessment, a PK interim evaluation included results from the SAD, MAD, and antidrug antibody (ADA) cohorts. Due to ongoing PK sample analysis, limited results are available from the AD patient cohort. In general, the PK results show BSI-045B is well behaved over the dose range used in this study for the SAD, MAD and AD patient cohorts.

For the SAD cohort, mean semilogarithmic plots of serum BSI-045B concentration (ng/mL) versus time (days) profiles for 6 subjects at 4 dose levels showed a typical absorption pattern for an IgG monoclonal antibody. BSI-045B has a mono-exponential decline and an apparent linear disposition following a 120, 240, 480, and 720 mg SC single injection. In general, the variability was typical of an IgG monoclonal antibody and given the low number of subjects.

A box plot analysis clearly determined dose proportionality and a linear disposition for both C_{max} and the area under the serum drug concentration-time curve from last dose extrapolated to infinity (AUC_{inf}) over the dose range. C_{max} values from the lowest single dose (120 mg) to the highest single dose (720 mg) ranged from 10.2 to 53.8 µg/mL, respectively. Time to maximum serum drug concentration (T_{max}) values ranged from 128 to 164 hours. The mean AUC_{inf} values increased in a dose -proportional manner between the 120 mg and the 720 mg dose and mean values ranged from a low of 362.8 to 2066 day*µg/mL. The mean apparent terminal elimination half-life ($t_{½}$) values were consistent and varied between 24.3 and 29.5 days, which is a typical half-life for an IgG monoclonal antibody.

In the MAD cohort, the mean semilogarithmic plots of serum BSI-045B concentrations (ng/mL) versus time (days) profiles were constructed for subjects receiving active drug (N=6) following the 240 mg SC dose Q7D for 5 doses and the 480 mg SC doses Q7D for 3 doses. The mean profile for the 240 mg multiple doses showed a typical PK profile for an IgG monoclonal antibody administered Q7D for 5 doses, with the mean trough serum BSI-045B concentrations continuing to rise over the dosing period in the expected manner. Steady-state conditions were not attained since only 5 doses were administered. Following peak drug concentrations, BSI-045B followed a mono-exponential decline over time. For the 480 mg SC dose, Q7D dosing for 3 doses showed a similar and a typical rise in serum BSI-045B concentration versus time profile. Following the third dose and after attainment of C_{max}, there was an apparent mono-exponential decline.

5.2.3.3.1 Part C1: 240 mg Q7D SC Dose

Nine subjects completed Cohort C1: first dose and 7 subjects had serum drug concentration vs time data that were used for PK analysis. Following the first dose of 240 mg, the mean C_{max} value was 17.6 µg/mL which was close to the C_{max} mean value (19.9 µg/mL) determined in the SAD cohort at the same SC dose level. The T_{max} mean value was 147 hours which compares favorably with the mean value of 164 hours determined in the SAD cohort. The mean area under the serum drug concentration-time curve (AUCτ) value was 93.5 day*µg/mL.

Following Q7D dosing for 5 consecutive doses in 6 subjects, the mean C_{max} was 76 µg/mL and occurred at 776 hours. The mean C_{max} value was close to the expected mean value of 88 µg/mL (mean C_{max} from first dose * 5 doses), confirming a linear disposition of BSI-045. The mean C_{min} value was 54.9 µg/mL and the mean average serum drug concentration (C_{ave}) was 65.6 µg/mL. The mean AUCτ value was 458.9 day*µg/mL and was very close to the expected mean value of 468 day*µg/ml (mean AUCτ from first dose * 5 doses), again confirming a linear disposition of BSI-045. The mean AUC_{last} was 2455 day*µg/mL. The mean $t_{1/2}$ was 23.8 days and is similar to the half-lives determined in the SAD cohort. The mean value for RC_{max} (C_{max} of fifth dose/C_{max}) was 5.1 and the mean value for R_{auc} (AUCτ of fifth dose/AUC_{0-7}) was 6.1. The RC_{max} and R_{auc} would be expected to be 5. The mean values from the two parameters further support the linear disposition of BSI-045B.

5.2.3.3.2 Part C2: 480 mg Q7D SC Dose

Eight subjects completed Cohort C2: first dose and 6 subjects had serum drug concentration vs time data used for PK analysis. Following the first dose of 480 mg, the mean C_{max} value was 37.5 µg/mL which was very close to the C_{max} mean value (42.0 µg/mL) determined in the SAD cohort at the same dose level. The mean T_{max} value was 124 hours which compares favorably with the mean value of 128 hours determined in the SAD cohort. The mean AUC_{tau} value was 214.3 day*µg/mL.

Mean (± standard deviation [SD]) PK parameters were determined following Q7D dosing for 3 consecutive doses in 6 subjects. The mean C_{max} was 98.6 µg/mL and occurred at 432 hours (T_{max}). The mean C_{max} value was slightly below the expected mean value of 112.5 µg/mL (mean C_{max} from first dose * 3 doses), but still supports the linear disposition of BSI-045. The mean minimum observed serum drug concentration (C_{min}) value was 65.2 µg/mL and the mean C_{ave} (AUCτ/τ) concentration was 89.2 µg/mL. The mean AUCτ value was 624.2 day*µg/mL which was very close to the expected mean value of 643 day*µg/mL (mean AUCτ from first dose * 3 doses), again confirming a linear disposition of BSI-045. The mean AUC_{last} was 2454 day*µg/mL. The mean $t_{1/2}$ was 22.1 days and is similar to the half-life determined in the SAD and MAD C1cohorts. The mean value for RC_{max} (C_{max} of the third dose/C_{max}) is 2.7 and the mean value for R_{auc} (AUCτ of third dose / AUC_{0-7}) is 3.1. The RC_{max} and R_{auc} would be expected to be 3. The mean values further support the linear disposition of BSI-045B.

5.2.3.3.3 Part B: 480 mg SC Dose

Five AD patients are enrolled in the ongoing Part B of the study. Four of the 5 patients had serum drug concentration vs time data up to Day 15. Patients received a single SC dose of 480 mg of BSI-045B. C_{max} and T_{max} were determined over this time period. The mean C_{max} of BSI-045B from 4 patients was 41.0 µg/mL and was nearly identical to the mean C_{max} value of 42.0 µg/mL determined in the SAD cohort and is close to the mean C_{max} value of 37.5 µg/mL determined in the 480 mg first dose in the MAD cohort. The T_{max} mean value was 108 hours, shorter than the mean half-life of 128 hours and 124 hours reported in healthy volunteers following a 480 mg dose in the SAD cohort and following the first 480 mg SC dose in the MAD cohort.

5.2.3.4 Anti-drug Antibodies

The presence of ADAs in patients with AD enrolled in Part B have not been evaluated at the present time. In Part A (SAD), ADA was detected in 1 subject at the 120 mg, 240 mg and 720 mg dose levels. There were no occurrences of ADA at the 480 mg dose. In total, 3 subjects out of 24 subjects in Part A had ADA present and in 2 out of 3 occurrences, ADA appeared late in the study. In Part C, 2 out of 6 subjects developed ADA at the last scheduled PK sampling on Day 124 following administration of 5 doses of 240- mg Q7D. Following administration of 480 mg SC Q7D for 3 doses, no ADA was detected over the 124-day study period. The results suggest a low incidence of ADA following single and multiple dosing.

In general, the PK analysis has shown BSI-045B is well behaved following single and multiple doses in subjects. While there were minor apparent differences among various cohorts in their PK parameters, given the sample sizes and individual variances, the assessment of dose proportionality clearly showed a linear disposition of BSI-045B over the dose range from 120 mg to 720 mg in the SAD cohort and dose proportionality was also confirmed in the MAD cohort. A single SC dose of 480 mg in the SAD and AD patient cohorts exhibited nearly identical mean C_{max} values. In general, the $t_{1/2}$ is approximately 25 days for subjects in the SAD and MAD cohorts. Results from the ADA assessment show a low incidence of ADA in both the SAD and MAD cohorts. The consistent and reliable PK profiles of BSI-045B observed in the SAD and MAD cohorts has provided a basis for designing a dose regimen in the proposed proof-of-concept Phase 2 study.

5.2.4 Design of Phase 2 Studies

This IND-enabling Phase 2a study is specifically designed to be a small, simpler study to give the Sponsor early insights into the activity of this molecule in a patient population after multiple dosing. This study is not intended to take the place of or to be a definitive Phase 2b study. A definitive Phase 2b study, using multiple doses and dosing regimens, will be conducted after we have more information about the product's effects in the AD patient population from the Phase 2a study. Prior to proceeding to Phase 3, the Sponsor will conduct both this Phase 2a study as well as a Phase 2b study.

5.3 Product Name

Generic name: BSI-045B

Molecular formula: $C_{6470}H_{9968}N_{1708}O_{2020}S_{46}$ (no post-translational modifications)

Molecular weight: 145,183 Da (N-terminal cyclization of heavy chain, excision of C-terminal lysine of heavy chain, aglycosylated)

Active ingredient: BSI-045B protein

Dosage form: Injection, 300 mg/vial (2.5-mL/vial, 120 mg/mL)

Excipients: histidine, acetic acid, proline, polysorbate 80 (for injection), water for injection

Note: The product pH is 5.8 ± 0.5.

5.4 Study Rationale

AD is a common inflammatory skin disorder characterized by recurrent eczematous lesions and intense itch. It is a major non-communicable disease that affects both children and adults and is the leading cause of the global burden from skin disease (Langan et al, 2020). It is estimated that 1 in 10 individuals will develop eczema during their lifetime. Eczema impacts people of all skin colors, races, and ethnicities (range 10 to 13%) (National Eczema Association).

AD involves a complex interplay of inflammatory pathways with multiple cytokines and inflammatory and epithelial cells implicated, with AD lesions always associated with underlying immune activation. Alarmins, which include TSLP, are endogenous, constitutively expressed chemotactic and immune activating peptides that are released following degranulation, cell injury or upon immune induction (Yang et al, 2017). TSLP is an IL-7-like cytokine expressed by epithelial cells and keratinocytes, and a key instigator of the immune response to environmental insults, initiating a range of downstream inflammatory pathways (Gauvreau et al, 2020). A common symptom of pruritis observed in AD can be attributed to TSLP signalling indirectly via the aforementioned inflammatory cascade but also via direct activation by TSLP of a specific subset of sensory neurons expressing TSLPR and the ion-channel transient receptor potential ankyrin 1 (TRPA1), further validating the targeting of TSLP in AD therapies (Wilson et al 2013). BSI-045B is designed to inhibit TSLP binding to the TSLP receptor, thereby inhibiting the inflammatory cascade and direct activation by TSLP of a specific subset of sensory neurons expressing TSLPR and the ion-channel TRPA1 associated with atopic dermatitis.

Anti-TSLP therapy has been clinically validated and is an effective treatment for allergic inflammatory diseases such as severe asthma (Menzies-Gow et al, 2021) and has shown clinical activity in patients with moderate to severe atopic dermatitis (Parnes et al, 2019). In vitro studies with BSI-045B demonstrated that the IP inhibits the TSLP pathway and

production of downstream cytokines. BSI-045B is an anti-TSLP mAb being investigated to treat moderate to severe AD.

In animal models, BSI-045B reduced levels of inflammatory factors and eosinophil production in a dose-dependent manner. In preclinical studies, BSI-045B was safe and well tolerated, and no treatment-related abnormal changes were observed during administration and recovery. BSI-045B is not associated with irritation at the injection site and has a low incidence of immunogenicity.

This study is a Phase 2a, multicenter, proof-of-concept clinical trial to evaluate efficacy and safety of BSI-045B mAb injection in patients with moderate to severe atopic dermatitis. The study will also evaluate the tolerability, PK, immunogenicity, and PD/biomarker of BSI-045B following SC injections. The findings from this proof-of-concept study will be used to design a follow-on Phase 2b study.

5.5 Proposed Strengths and Dose Justification

Good Laboratory Practice (GLP) toxicity studies conducted with BSI-045B in cynomolgus monkeys showed that the IP is well tolerated up to 600 mg/kg (more than 16-fold the human equivalent dose for the maximum single dose (720 mg) administered in the Phase 1 clinical study) when administered as a single dose by SC injection. Further evaluation of the toxicity of BSI-045B was performed through a GLP repeat dose study (TQC-TOX-01) in which 5 doses of BSI-045B were administered SC to cynomolgus monkeys with a 1-week interval between administrations, followed by a 4-week recovery period. Doses of 30, 100 and 300 mg/kg were administered, with the high dose administered giving a human equivalent dose 19.4-fold higher than the clinical dose (300 mg) to be administered in the Phase 2a clinical trial. As in the single-dose study, no relevant toxicity findings were observed that were attributable to BSI-045B and the no observed adverse effect level (NOAEL) was considered to be 300 mg/kg for repeat dose administration up to 5 cycles. No significant toxicity findings were observed following weekly SC administration of BSI-045B to cynomolgus monkeys at 15, 50, and 150 mg/kg for 26 consecutive weeks. The NOAEL of BSI-045B was considered to be 150 mg/kg over 26 consecutive weeks, with an HED of 2,903 mg for a 60-kg subject, resulting in a safety margin of 9.7-fold above the clinical dose (300 mg) to be administered in the Phase 2a clinical study.

Local tolerance assessment revealed no BSI-045B related abnormalities on clinical or microscopic evaluation of the injection site, and immunotoxicity evaluation revealed no noteworthy findings.

No sex-related effect in the toxicity of BSI-045B after SC administration was evident in the nonclinical studies performed in monkeys (BSI-045B Investigator's Brochure). Nonclinical pharmacology studies have demonstrated BSI-045B's efficacy in binding, in a highly specific manner, to human TSLP in vitro. BSI-045B was also shown to inhibit the ability of TSLP to bind to its target receptor in an in vitro cell based model, using TSLPR expressing HEK293 cells. (BSI-045B Investigator's Brochure). Like BSI-045B, tezepelumab is a monoclonal antibody that specifically binds to human TSLP and acts on the same target as BSI-045B.

Parnes et al (2019) reported results from a Phase 1 study in which tezepelumab was administered as a single SC dose (2.1, 7, 21, 70, 210, or 420 mg) or an intravenous (IV) dose (210 or 700 mg) to healthy subjects and following SC injections in multiple dose regimens of 35, 105, 210 mg or IV injections of 700 mg over a 3-month period. Parnes also reported results from a single IV injection of 700 mg in AD patients. In addition, Parnes and Sakamoto et al (2020) conducted independent phase 1 PK studies and determined that tezepelumab followed a linear disposition over various SC dosing levels and dosing intervals (including Q7D) up to 3 months.

Parnes et al (2019) reported mean PK parameter values for C_{max} and AUC over the dosing interval following an IV dose of 700 mg of tezepelumab administered Q28D over 3 months. The reported C_{max} was 370 µg/mL and the AUC was 4050 day*µg/mL. Following a single highest SC dose of 420 mg, the mean C_{max} was 58 µg/mL and AUC_{inf} was 2140 day*µg/mL or 51360 h*µg/mL Parnes also reported no differences between HVs and AD patients in mean values of various PK parameters. Zheng et al (2021) reported that although PK parameter values were slightly lower following SC injection into the arm, and there were no clinically significant differences between arm, abdomen, and thigh injections following an SC vial and syringe injection of 210 mg tezepelumab.

Simpson et al (2018) reported results from a Phase 2a, randomized, double-blind, placebo-controlled study at 26 centers in Australia, Canada, Germany, Hungary, New Zealand, and the United States. The 12-week study evaluated the efficacy and safety of tezepelumab in patients with moderate to severe AD who were treated with continuous concomitant class 3 topical corticosteroids (TCS). The effects of tezepelumab in patient-reported outcomes and impact of serum biomarkers on treatment responses were also reported. Following SC injections of 280 mg of tezepelumab every 2 weeks plus TCS, patients with moderate to severe AD achieved numerical improvements over placebo in the percent achieving 50% improvement on the EASI at week 12; however, these improvements were not statistically significant. In a safety analysis of the as-treated population (N=111), TEAEs were mild or moderate in severity (grade 1-2) and no deaths were reported. The most frequent TEAE that was considered by the investigators to be possibly treatment related was injection site erythema, which was reported in 3 (5.4%) of patients receiving tezepelumab and none in the placebo group. Numerical improvements were seen across several clinical and patient-reported endpoints, and greater efficacy in biomarker-defined subgroups suggested potential benefits in TSLP blockade. Simpson et al (2018) postulated that limitations of their study may have been confounded by the patient population selected (only 10% of patients had severe disease); patients were not required to be refractory to TCS at baseline, patients applied high-strength TCS during the 2-week run-in period, and the dose selected may not have provided a complete inhibition of TSLP. This study will investigate the safety, tolerability, PK, biomarkers, and impact of using higher SC doses of BSI-045B in AD patients than previously used with tezepelumab. Higher doses may increase receptor occupancy, leading to a more pronounced biomarker and clinical response. The study results will provide additional information that will be used to better design future studies investigating whether BSI-045B is associated with significant clinical effects.

For Study BSI-045B-002, the proposed SC doses of 300 mg administered weekly (QW) for 3 doses (loading dose) or twice weekly (Q2W) (maintenance dose) fall within the dose range of SC administration of 240 mg and 480 mg previously evaluated in a Phase 1 MAD study.

The dosing intervals proposed for Study BSI-045B-002, including QW/Q2W, are designed to meet or exceed the weekly (Q7D) interval investigated in the Phase 1 MAD study. In that study, BSI-045B was observed by a mono-exponential reduction in concentration after reaching peak levels. According to the principle of superposition, which is generally applicable in such cases, the concentration levels following each dose are expected to be superimposed on the levels after the prior dose. With these proposed dosing intervals being equal to or longer than those in the MAD study, the peak concentrations of the drug in Study BSI-045B-002 are anticipated to be similar to or lower than those in the MAD study. This implies that, if peak drug concentration is a key factor in toxicity, the safety profile of the proposed dosing regimen in Study BSI-045B-002 should be comparable to, or more favorable than, what was observed in the Phase 1 MAD study. A detailed evaluation of the PK characterization from Study BSI-045B-001 is presented in Section 5.2.3.3.

5.6 Risks and Benefits of BSI-045B in Human Volunteers Patients with Atopic Dermatitis

Good Laboratory Practices (GLP) toxicity studies conducted with BSI-045B in cynomolgus monkeys showed that the drug is well tolerated up to 600 mg/kg (more than 16-fold the human equivalent dose (HED) for the maximum single dose (720 mg) administered in the Phase 1 clinical study) when administered as a single dose by SC injection. Further evaluation of BSI-045B's toxicity was performed through a GLP repeat dose study (TQC-TOX-01) in which 5 doses of BSI-045B were administered SC to cynomolgus monkeys with a 1-week interval between administrations, followed by a 4-week recovery period. Doses of 30, 100 and 300 mg/kg were administered, with the high dose administered giving an HED 19.4-fold higher than the clinical dose (300 mg) to be administered in the Phase 2a clinical trial. As in the single dose study, no relevant toxicity findings were observed that were attributable to BSI-045B and the NOAEL was considered to be 300 mg/kg for repeat dose administration up to 5 cycles. Additionally, a 26-week GLP toxicity study with an 8-week recovery period in sexually mature cynomolgus monkeys was conducted. Monkeys were dosed with BSI-045B SC at 0, 15, 50 or 150 mg/kg/week. No significant toxicity findings were observed following weekly SC administration of BSI-045B to cynomolgus monkeys at 15, 50, and 150 mg/kg for 26 consecutive weeks. The NOAEL of BSI-045B was considered to be 150 mg/kg over 26 consecutive weeks, with an HED of 2,903 mg for a 60-kg subject, resulting in a safety margin of 9.7-fold above the clinical dose (300 mg) to be administered in the Phase 2a clinical study.

Local tolerance assessment revealed no abnormalities attributable to BSI-045B on clinical or microscopic evaluation of the injection site, and immunotoxicity evaluation revealed no noteworthy findings.

Biosion Australia Pty Ltd is currently completing a Phase 1 study in Australia. The study consists of 3 parts: Part A, a SAD study in HVs; Part B, a single-dose study in patients with AD; and Part C, a MAD study in HVs. An interim analysis was conducted to analyze the

safety and PK data. In the interim analysis, a total of 54 participants, including 28 (51.9%) men and 26 (48.1%) women, were assessed. The actual numbers of subjects in Part A Cohort 1 (120 mg), Cohort 2 (240 mg), Cohort 3 (480 mg), and Cohort 4 (720 mg) were 8, 8, 8, and 8; the actual number of patients in Part B was 5; the actual number of subjects in Part C Cohort 1 (240 mg Q7D) was 9, and Cohort 2 (480 mg Q7D) was 8.

According to the interim analysis for this Phase 1 study, there were no serious TEAEs, TEAEs leading to death, or any deaths in any part of the study. There was 1 (1; 12.5% of group) severe TEAE (transaminases increased), reported by a subject in the 240-mg dose level Cohort in Part A. One subject (1; 11.1% of group in Part C; 240-mg Q7D Cohort) was withdrawn from the study due to TEAEs (increased AST and increased ALT).

Overall, the frequency of TEAEs was similar across all single and multiple dose levels, with most or all subjects in each cohort in Part A (SAD) and Part C (MAD) reporting at least 1 TEAE. In Part A, the frequency of study drug related TEAEs increased with dose level, indicating a potential relationship. In Part C, there was no increase in the frequency of study drug related TEAEs increasing with dose level. The frequency of TEAEs in Part B (patients with AD; 2 [40.4%]) was lower than the frequency of TEAEs at the same dose level in healthy volunteers in Part A (480 mg; 7 [87.5%]).

Treatment-emergent AEs in SOC General Disorders and Administration Site Conditions, most or all of which were injection site reactions, were the most common TEAEs by SOC in both Part A and Part C. A relationship between increasing dose level and the events injection site erythema and injection site pain was observed in Part A, and a relationship between increasing dose level and injection site swelling was observed in Part C. In Part B, no TEAE by Preferred Term was reported by greater than 1 (20.0%) of subjects. Except for the severe TEAE in Part A, all TEAEs in the study were mild or moderate.

Overall, injection site reactions were common in Part A and Part C of the study, although variances in the frequency and nature of reactions across dose levels were observed. Remarkably, in Part B no patients with AD reported injection site reactions on the day of study drug administration; 1 subject (20.0%) reported an injection site reaction (mild tenderness) on Day 2. Based on the clinical safety information of similar targeted drugs, injection site reactions are common adverse reactions, which could be regarded as potential risks for receiving BSI-045B treatment (Adbry® prescribing information, 2022).

Another Phase 1 study was conducted by an independent licensee (CTTQ) for BSI-045B (named as TQC2731 by CTTQ) in healthy adults to evaluate the safety, tolerability, PK, and immunogenicity of TQC2731. As listed in the study abstract submitted to the American Academy of Allergy Asthma and Immunology meeting 2023, 54 participants were enrolled. TQC2731/placebo-related AEs were mild or moderate in severity across all dosing groups. The incidence of AEs observed was not dose dependent. No drug-related SAEs were reported. In summary, TQC2731 was safe and well-tolerated (Liu et al, 2023).

Thus, based on both nonclinical and clinical data obtained with BSI-045B, this new monoclonal antibody is expected to be well tolerated in the proposed Phase 2a study. Up to

this amendment to the study protocol, no specific safety signals have been observed in this study, indicating a safety profile of 300 mg monotherapy in AD patients.

6 STUDY OBJECTIVES AND ENDPOINTS

Table 5. 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

Objectives	Endpoints
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

7 INVESTIGATIONAL PLAN

This 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/biomarker 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.

7.1 Study Dosing

The total number of evaluable patients with AD will be approximately 20 to 24.

Patients will initially be treated with a loading dose of BSI-045B given QW for 4 weeks. Thereafter, BSI-045B will be given at Q2W interval to Week 24.

7.2 Washout Period

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 Table 6. Eligible patients who complete the washout period for previous therapies for AD will be treated with BSI-045B.

Washout period is required for patients already on treatment for AD. Washout duration requirements is described in Table 6.

Table 6. Washout Durations Required Before Initial Dose of BSI-045B, by Therapy

Therapy	Washout Duration Required before First Dose of BSI-045B
Tralokinumab	12 weeks
Dupilumab	12 weeks
Phototherapy	4 weeks
Abrocitinib	4 weeks
Upadacitinib	4 weeks
Topical corticosteroids	1 week
Topical calcineurin inhibitors	1 week
Investigational Products	4 weeks
All Other Therapies prescribed for therapeutic immunosuppression or immunomodulation	3 weeks or 4 half-lives, whichever is longer

7.3 Replacement of Patients who Withdraw from Treatment

Patients who do not complete the first 5 doses of BSI-045B will be replaced.

7.4 Monitoring by Safety Steering Committee

The Safety Steering Committee (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 serious adverse events (SAEs) that might prompt a change to the study.

7.5 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), compared with baseline (Day 1).

7.6 Other Efficacy and Safety Assessments

Additional efficacy outcomes will include other scores on EASI, Investigator's Global Assessment (IGA), Facial IGA, assessment of conjunctivitis, and Peak Pruritus Numerical Rating Scale (PP-NRS). Efficacy assessments will be conducted prior to dosing on Day 1, at all subsequent visits, and at the time of early withdrawal from the study.

Adverse events (AEs) will be collected after signing the ICF and throughout the Treatment Period and the Follow-Up Period. After injections, all patients should be monitored at the study sites for at least 30 mins to observe body reactions, including injection site reactions. Any injection site reactions observed after each site visit should be reported to the Investigators by the patients.

Concomitant medications will be recorded after signing the ICF and throughout the Treatment Period and Follow-Up Period.

During the Treatment and Follow-up Periods, PK and PD samples will be collected for analysis. Immunogenicity will be assessed throughout the Treatment Period and Follow-up Period.

Follow-up assessments will occur during subsequent visits to the study sites. At the Investigator's discretion, patients may return to the study sites at other times for re-evaluation.

7.7 Follow-up Period

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

7.8 Study Drug Administration

The preferred SC injection site is the abdomen. The thigh can be used as an alternative site for SC injections. A 2.5 mL injection of 120 mg/mL (300 mg total dose) will be administered at a single injection site.

7.9 Enrollment and Study Procedures

7.9.1 General Considerations

Patients will be assigned a screening identification number once they have signed the ICF and will then be considered enrolled into the study if they have been determined to satisfy all inclusion and exclusion criteria (and after washout if requiring washout).

When collecting PK samples, immunogenicity, PD/biomarker, and clinical laboratory samples, vital signs, and/or ECG assessments are scheduled to occur at the same time point, ECG and vital signs testing will be performed prior to blood collections. The preferred order of assessments is:

1) ECG
2) Vital signs
3) PK, Immunogenicity, PD/biomarker sampling
4) Clinical laboratory sampling

Samples for serum PK (collected at nominal times), ADA, and PD/biomarker assessments will be collected for PK and ADA assessments using GLP validated assays and for PD/biomarker assessments using fit-for-purpose, qualified assays with commercial kits. Refer to the laboratory manual for additional details on laboratory assessment and sample processing.

7.9.2 Assessments at Screening

Screening assessments will be performed after the patients signed the ICF. After all screening results are obtained, eligible patients who require no washout will be enrolled to the study directly; eligible patients who require washout will start washout and repeat some screening assessments during Day-14 to Day-1.

Rescreening is allowed after a delay of at least 4 weeks from the initial screening assessment. Any rescreening should be approved by the Sponsor.

A complete history will be recorded at Screening and will include medical history, surgical history, smoking history, alcohol use history, drug abuse history, prior and current medication, blood donation history, allergy history, and other demographic information.

Physical examinations at Screening will include weight, height, and body mass index (BMI), as well as a complete examination. Symptom-driven examinations will be performed at other time points.

Other screening assessments will include 12-lead ECG, blood pregnancy test (females of childbearing potential only), and vital signs (blood pressure, pulse, temperature, and

respiratory rate). A subset of these tests will be completed at other time points, as detailed in the Schedule of Activities.

A screening for drugs of abuse is optional (per the discretion of the Investigator).

Clinical laboratory assessments at Screening will include those listed in Table 7 and will be conducted as site policy requires.

Table 7. Clinical Laboratory Assessments, BSI-045B-002

Type of Test	Laboratory Parameters
Hematology	Hemoglobin, hematocrit, WBC count and differential, RBC count and indices, platelet count
Chemistry	Sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, glucose, BUN, creatinine, uric acid, ALT, AST, GGT, alkaline phosphatase, total protein, albumin, globulin, total bilirubin, LDH, total cholesterol, triglycerides
Coagulation	PT, aPTT, fibrinogen, INR
Virology (performed only at Screening)	HbsAg, anti-HCV, HIV
Urinalysis	Protein, glucose, ketones, occult blood, urobilinogen, urine sediment microscopy (if other parameters abnormal)

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; ECG = electrocardiography; GGT = gamma glutamyl transferase; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PCR = polymerase chain reaction; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

7.9.3 Efficacy

Patients will be assessed to determine an EASI score at Screening, prior to dosing on Day 1 (baseline), at subsequent visits, and at the time of early withdrawal from the study.

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 (Hanifin and Rajka, 1980). The primary efficacy endpoint is the proportion of patients with ≥EASI75 at Week 26 (2 weeks after last dose at Week 24).

The IGA and facial IGA require the Investigator to rate the severity of AD on a scale from 0 (clear) to 4 (severe).

The assessment tool for itching is the PP-NRS, on which the patient 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. Patients will complete the rating scale daily using the patient diary beginning on Day -8, throughout the last study visit, and at the time of early withdrawal from the study. In order to calculate an average for the score, the patient must have completed the diary for a minimum of 4 days during the previous 7 days.

Exploratory efficacy and safety assessments will include the following. At each visit, the percentage of patients who achieve 50%, 75%, and 90% improvement in the EASI score from Day 1) and the change in EASI score from Day 1 will be calculated. Detailed analysis of all exploratory endpoint is described in the Statistical Analysis Plan (SAP).

- 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 IGA 0 or 1 Week 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

7.9.4 Safety

The safety of BSI-045B will be assessed by the incidence of AEs, anti-BSI-045B ADA formation, clinical laboratory evaluations, 12-lead ECGs, vital signs, physical examinations, occurrence of conjunctivitis, as well as injection site reactions. The relationships between study medication and AEs will be evaluated by the Investigators.

Assessments will occur during visits to the study sites or via videoconference or telephone conference. Adverse events will be collected throughout the Treatment Period and the Follow-Up Period to determine whether there are ongoing AEs, SAEs, worsening of AEs or SAEs, or development of new AEs or SAEs. Follow-up of AEs and SAEs will occur during clinic visits and whenever abnormal, clinically significant findings are observed. Concomitant medications taken after the final dose of BSI-045B will be recorded throughout the Follow-Up Period. At the Investigator's discretion, patients may be brought back to the study sites at other times for re-evaluation.

For the assessment of conjunctivitis, conjunctivitis history will be asked at screening visit, and all patients will be asked if they had been diagnosed as conjunctivitis at every visit during study treatment period. For patients who have been diagnosed as conjunctivitis, the conjunctivitis severity will be asked, and the severity grades include: 0 = no conjunctivitis; 1

= mild conjunctivitis; 2 = moderate conjunctivitis requiring treatment; 3 = severe conjunctivitis that may require an ophthalmic exam. Investigators should also check the patients' eyes and record any findings.

7.9.5 Stopping Criteria

If a patient experiences an AE assessed as ≥ Grade 3 (≥ Grade 2 for the system-organ class of Cardiac Disorders) according to Common Terminology Criteria for Adverse Events (CTCAE v5), then: 1) BSI-045B treatment may be continued if the AE is considered to be unrelated to BSI-045B; 2) BSI-045B treatment will be withheld if the AE is considered to be related to BSI-045B, until the toxicity returns to ⩽ Grade 2; 3) BSI-045B will be permanently discontinued if the AE recurs to ⩾ Grade 3 after BSI-045B treatment resumed and is considered to be BSI-045B related. Treatment discontinuation decisions will be made by Investigators after a discussion with Sponsor. These AEs include hepatotoxicity, injection site reactions, allergic conjunctivitis and hypersensitivity (see Table 8). Patients who experience such AEs will be followed until the adverse events resolves or stabilizes. Study drug administration will not be discontinued.

If 2/3 of patients experience any adverse event assessed as ≥ Grade 3 (≥ Grade 2 for the system-organ classes of Cardiac Disorders) per Common Terminology Criteria for Adverse Events (CTCAE v5), the study should be suspended for an evaluation from SSC.

Table 8. Toxicity with the Potential to Cause Study Treatment Discontinuation

Toxicity	Criteria
Hepatotoxicity	• AST/ALT >5×ULN and/or Bilirubin >3×ULN • Hepatic failure • Recurrence of a severe or life-threatening event, or any of the laboratory abnormalities listed above, that are presumed to be study treatment related.
Injection site reactions	• Ulceration or necrosis; severe tissue damage; operative intervention indicated • Severe reactions lasting more than 24 hours
Conjunctivitis*	• Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care Activities of Daily Living (ADL); if infectious is the etiology, intravenous antibiotic, antifungal, or antiviral intervention indicated • Urgent intervention indicated or life-threatening.
Hypersensitivity	• Anaphylaxis: Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension

Toxicity	Criteria
	• Serum sickness: Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated • Allergic reaction: Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated • Urgent intervention indicated or life-threatening.

* Definition of Conjunctivitis: a disorder characterized by inflammation, swelling and redness of the conjunctiva of the eye.

For the evaluation of injection site reactions, the following scale (Table 9) which is a part of FDA toxicity grading scale will be used.

Table 9. Grading scale for injection site reactions

Local reactions	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Pain	Dose not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling **	2.5-5 cm and dose not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

7.9.6 Pharmacokinetic Assessments

Assessments of the PK of BSI-045B will be evaluated throughout the Treatment Period and Follow-up Period as outlined in the Schedule of Activities in Section 3. Blood sample for the analysis of the PK of BSI-045B will be collected at the time points indicated in the PK Sample Collection in Table 1 and Table 2. Refer to the laboratory manual for additional details on laboratory assessment and sample processing.

7.9.7 Immunogenicity

Assessments of the ADA status (negative or positive with titer) of BSI-045B will be evaluated throughout the Treatment Period and Follow-up Period as outlined in the Schedule of Activities in Section 3. Blood sample for the analysis of the ADA of BSI-045B will be collected at the time points indicated in the Immunogenicity Sample Collection in Table 1 and Table 2. Refer to the laboratory manual for additional details on laboratory assessment and sample processing.

7.9.8 Pharmacodynamic Biomarker Assessments

Blood samples (4 mL) for TARC/CCL-17, periostin, and IgE concentrations will be collected at W1D1, W2, W3, W4, W8, W12, W16, W20, and W24 within 1 h before each dose during the Treatment Period, on every visit during the Follow-up Period, and at the time of early withdrawal from the study drug.

7.10 Criteria for end of Study

A patient is considered to have completed the study when study and follow-up procedures have been completed as per the Schedule of Activities.

The end of this study is defined as the date when the last patient, last visit occurs or when last patient finished the safety follow-up, whichever occurs first.

7.11 Criteria for Early Discontinuation of Study Drug

A patient has the right to withdraw from treatment at any time at his/her request and this decision will not affect the treatment provided by clinicians or research institutions in the future. Moreover, the patients may be withdrawn at any time at the discretion of the Investigators for safety, behavioral, compliance, or administrative reasons. When medically feasible, the Medical Monitor should be consulted prior to study drug discontinuation. Study drug treatment will be permanently discontinued if one of the following criteria applies:

- Withdrawal of consent
- Patient or guardian requests to discontinue the study drug
- Start of new anti-AD treatment
- Lost to follow-up
- Death
- Intolerable safety issues

- AE, abnormal laboratory tests, or other medical condition (including pregnancy) occurred, and the Investigator judges that the study drug should be terminated based on the best interests of the patient
- Major noncompliance with the study protocol and in the Investigator's judgment, treatment should be discontinued
- Other conditions that the Investigator considers inappropriate for continue treatment
- Study terminated by the Sponsor

If a patient withdraws from study treatment after receiving study treatment, a safety examination is required within 7 days after the patient's withdrawal. Additional follow-up assessments should be completed.

7.12 Criteria for Withdrawal from the Study

The primary reason for withdrawal from the study will be recorded as one of the following:

- Death
- Lost to follow-up
- The patient has poor compliance and serious deviation from study protocol
- Withdrawal of consent by patient
- Study terminated by Sponsor or regulatory agency
- Other conditions as per Investigators

The Investigator or designee must make appropriate efforts to contact any patient who is lost to follow-up, with at least 3 telephone contacts. If a patient who has received study drug withdraws from the study early, a safety examination is required within 7 days after the patient's withdrawal if the patient consents to this visit.

7.13 Data Handling for Patients who do not Complete the Study

Before descriptive statistical analysis of data, the Investigator and the Sponsor will determine whether individual patients are to be included in a per-protocol analysis for the analysis of the primary efficacy endpoint. Patients who receive any amount of study drug will be included in safety analyses.

7.14 Compliance/Adherence

In select cases, the Investigator may need to discuss with the patient whether they should continue the study and make relevant explanations in certain situations, including but not limited to the following:

1) The Investigator considers it advisable for the patient to stop the study from the perspective of medical ethics, or believes that withdrawal from the study may be in the best interest of the patient.

2) During the study, the patient does not comply with the study plan and shows poor compliance (eg, failure to take the study drug or failure to obtain samples for PK and safety evaluation as required by the protocol).

3) The patient evidences behavioral issues during the study that may affect study assessments

7.15 Randomization and Blinding

The study will not be randomized and will be unblinded.

8 STUDY POPULATION

8.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1) In the opinion of the Investigator, the patient is capable of understanding and complying with protocol requirements.
2) The patient signs and dates a written ICF prior to the initiation of any study procedures.
3) The patient has a diagnosis of AD (according to the criteria established by Hanifin and Rajka, 1980). The diagnosis of AD must have been present for at least 6 months.
4) The patient is aged 18 to 65 years, inclusive at the time of consent. Patients of any gender are eligible.
5) A female patient weighs at least 45 kg and a male patient weighs at least 50 kg. The patient has a BMI between 18.0 and 32.0 kg/m^2 inclusive at Screening.
6) The EASI is ≥12 at Screening and on Day 1.
7) The score on the IGA is ≥3 (scale of 0 to 4) at Screening and on Day 1.
8) The total body surface area (BSA) affected by AD is ⩾10% as assessed by the physical examination at Screening and on Day 1.
9) The patient has:

   (a) not received prior treatment with topical or systemic medications OR

   (b) the patient has active disease despite topical or systemic treatment as per the Investigator at the time of screening.

   Prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products can be allowed if the patient agrees to continue using at the current dose during the study.
10) A male patient who is non-sterilized and sexually active with a female partner of childbearing potential agrees to use highly effective contraception from the time of signing the ICF throughout the duration of the study treatment and for 90 days (~5 half-lives) after the last dose of study drug (See Section 8.3).
11) A female patient of childbearing potential who is sexually active with a non-sterilized male partner agrees to use highly effective contraception from the time of signing the ICF throughout the duration of the study treatment and for 90 days after the last dose of study drug (See Section 8.3).
12) The patient has a negative urine/blood result for drugs of abuse (if there are concerns in the opinion of the Investigators regarding the use of illicit drugs, including cannabinoid products).

8.2 Exclusion Criteria

Any patient who meets any of the following criteria will be excluded from the study:

1) The patient has received any of the following treatments but did not finish the required washout period as stated in the following table. After the washout period, the patients can be considered for study treatment.

Therapy	Washout Duration Required before First Dose of BSI-045B
Tralokinumab	12 weeks
Dupilumab	12 weeks
Phototherapy	4 weeks
Abrocitinib	4 weeks
Upadacitinib	4 weeks
Topical corticosteroids	1 week
Topical calcineurin inhibitors	1 week
Investigational Products	4 weeks
All Other Therapies prescribed for therapeutic immunosuppression or immunomodulation	3 weeks or 4 half-lives, whichever is longer

2) The patient has another dermatologic condition that might confound a diagnosis of AD or a treatment assessment.
3) The patient has any clinically significant illness that may affect the safety, increase the risk for seizure or lower the seizure threshold, or potentially confound the study results, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality. It is the responsibility of the Investigator to assess the clinical significance of a patient's condition; however, consultation with the Sponsor's Medical Monitor may be warranted.
4) The patient has abnormal laboratory values during the Screening Period: ALT and/or AST > 1.5 times the upper limit of normal (ULN), total bilirubin ≥ 1.5 mg/dL, estimated glomerular filtration rate (GFR) < 60 mL/min (based on Cockcroft-Gault calculation), hemoglobin (Hgb) ≤ 10 g/dL, platelet count ≤ 150 $\times 10^3/\mu L$. Individual exceptions may be granted with the agreement of the Sponsor and the Investigator.
5) The patient has a history of anaphylaxis following biologic therapy.
6) The patient has a history of allergy to corticosteroids, diphenhydramine, hydroxyzine, cetirizine, or fexofenadine.
7) The patient has a history of a clinically significant infection within 4 weeks prior to Screening.
8) The patient has been diagnosed with a helminthic parasitic infection within 6 months prior to Screening.
9) The patient has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening or is unwilling to agree to abstain from excessive alcohol consumption and drugs (including cannabinoids) throughout the study.
10) The patient had a major surgical or major dental procedure within 8 weeks prior to Screening.

11) The patient is pregnant or lactating or intends to donate ova before, during, or within 90 days (~ 5 half-lives) since the last dose of study drug.

12) If male, the patient intends to donate sperm during this study or within 90 days (~ 5 half-lives) since the last dose of study drug.

13) The patient has a history of neurologic abnormalities including abnormal electroencephalography, brain injury including traumatic injury, perinatal cerebropathy, postnatal brain damage, blood-brain barrier abnormality, and cavernous angioma.

14) The patient has a history of cerebral arteriosclerosis.

15) The patient has a history of cancer, except for adequately treated basal or squamous cell skin cancer or in situ cancers; or any other cancer from which the patient has been disease-free for at least 5 years prior to the first dose of study drug.

16) The patient has a positive test result for HbsAg, anti-HCV, a history of active tuberculosis, a positive test result for HIV, or a known history of HIV infection at Screening.

17) The patient has poor peripheral venous access.

18) The patient has donated or lost ≥ 450 mL of blood (including plasmapheresis) or had a transfusion of any blood product within 90 days prior to the first dose of study drug.

19) The patient has an abnormal (clinically significant) ECG at Screening and/or on Day1. Entry of any patient with an abnormal (not clinically significant) ECG must be approved and documented by signature of the Investigator. In the case of a corrected QT interval (Fridericia) (QTcF) > 450 ms or > 470 ms (patients with bundle branch block) or PR interval outside the range of 115 to 220 ms, assessment may be repeated once for eligibility determination at Screening and/or on Day1.

20) The patient has poorly controlled hypertension and is not considered suitable for participation in this study in the judgement of the Investigators at Screening and/or on Day1.

21) The patient has abnormal resting heart rate and is not considered suitable for participation in this study in the judgement of the Investigator at Screening and/or on Day1. Assessment is allowed to be repeated once for eligibility determination at Screening and/or on Day1 if deemed necessary.

22) The patient plans to use any other prohibited medication or undergo any prohibited procedure during the study. Oral antibiotics are permitted. Bleach baths are not permitted.

23) The patient has a risk of suicide on the Patient Health Questionnaire-2 (PH-2) or in the judgment of the Investigator, or the patient has made a suicide attempt or has a history of deliberate self-harm within 6 months prior to Screening.

24) The patient is compulsorily detained for a medical or psychiatric illness.

25) The patient or their immediate family are personnel at the study site.

26) The patient is unable to comply with restrictions and prohibited activities/treatments as listed in the study protocol.

8.3 Contraception Requirements

Women of childbearing potential must use a highly effective method of contraception from the time of giving informed consent until at least 90 days after the last dose of study drug. Women are considered to be of childbearing potential following menarche until becoming postmenopausal (defined as no menses for at least 12 months without an alternative medical cause) unless permanently sterile. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Males with partners who are females of reproductive potential must agree to use condoms, and their partners will use a highly effective contraceptive method from the time of informed consent and for 90 days after the last dose of study drug.

Highly effective forms of contraception for females are defined as:

- Combined (estrogen- and progestogen-containing) hormonal contraceptives that inhibit ovulation, including oral, intravaginal, and transdermal products
- Progestogen-only hormonal contraceptives that inhibit ovulation, including oral, injectable, and implantable products
- Intrauterine devices and intrauterine hormone-releasing systems
- Bilateral tubal occlusion (women)
- Male partner vasectomy or other method of surgical sterilization provided that the partner is the sole sexual partner of the study patient and the vasectomized partner has received medical assessment of the surgical success
- Sexual abstinence in men and women (ie, refraining from heterosexual intercourse during the entire period of risk association with the study drugs) when it is the preferred and usual lifestyle of the patient; periodic abstinence (such as calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), and the lactational menorrhea method are NOT acceptable methods of contraception.

The following methods of contraception are NOT considered highly effective:

- Progesterone-only oral hormonal contraception that does not inhibit ovulation
- Barrier methods with or without spermicide, or spermicide alone

9 STUDY DRUG SUPPLIES, DOSING, AND CONCOMITANT MEDICATIONS

9.1 BSI-045B

BSI-045B injection is manufactured in compliance and supplied by Wuxi, China. The drug substance and drug product are manufactured in compliance with Good Manufacturing Practices. All study drugs sent to the study sites will be labeled according to current Good Clinical Practice (GCP) and local Therapeutic Goods Administration requirements.

The strength is 300 mg/2.5 mL/vial/120 mg/mL. Target filling volume is 3.16 mL.

9.2 Receipt, Dispensing, Storage, and Return of Investigational Product

BSI-045B injection is provided free of charge by the Sponsor. The clinical research site is responsible for the storage, dispensing, and administration of the study drug under recommended conditions according to the approved study protocol. The drugs used in this study will be received, stored, and dispensed by the site pharmacist, and the receipt, administration, distribution, and return of the IP will be documented in accordance with the standard operating procedures of the site. The IP is sensitive to light and high temperatures and should be stored and transported at 2°C to 8°C, protected from light. At the end of the study, the Investigator or designee will return the packaging of all used drugs and the remaining unused drugs to the Sponsor.

9.3 Concomitant Medications

Concomitant medications for AE treatment are allowed during the study.

The use of female contraception medications is allowed.

Oral antibiotics are permitted.

Use of nonprescription eye lubricant drops is permitted.

If it is medically necessary to initiate concomitant medications during the study, they will be recorded on the Case Report Form (CRF) and the Medical Monitor and/or Sponsor might be notified. All medications taken within 30 days of Screening will be recorded on the appropriate CRF.

9.4 Rescue Medications for Exacerbations of Atopic Dermatitis

No rescue medication will be permitted during the study.

9.5 Prohibited Concomitant Medications

The use of any other investigational agent during the study is prohibited.

The following interventions are restricted from Screening through completion of the study:

1) Treatment with a live (attenuated) vaccine or any investigational drug

2) Treatment with topical emollients containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products (patients may continue to use stable doses of such moisturizers if initiated before the initiation of study drug but should not change to a different product during the study).

3) Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate, azathioprine, calcineurin inhibitors, etc.) within 2 weeks prior to and during treatment with the study drug. However, inhaled steroids are allowed.

The following procedures are prohibited during participation in the study:

1) Major surgical and major dental procedures

2) Phototherapy including facials

3) Tanning in a bed/booth

4) Bleach baths

9.6 Drug Compliance

During recruitment and the Screening Phase, the purpose of this study will be described in detail to fully inform the patient, along with basic information about the study drug, the protocol, the study procedures, the dosing regimen (eg, dose, route of administration, etc.), clinical observation, frequency and process of biological sample collection, potential risks of participating in the trial, compensation and indemnification, etc. Information included in the ICF will allow the patient to decide whether to participate in the study and will help to increase compliance with the study drug. Before administration of study drug, the patient number and dose of the patient will be checked. After administration, administration instruments will be checked and the remaining study drug and empty packages will be counted.

10 ADVERSE EVENT REPORTING

10.1 Definitions, Acquisition, and Recording of Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered study drug and which does not necessarily have a causal relationship with the treatment. An AE can therefore be an unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to study drug.

10.2 Definition of Serious Adverse Event

An event is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

1) Death
2) A life-threatening AE (places the patient at immediate risk of death)
3) Inpatient hospitalization or prolongation of existing hospitalization
4) A persistent or significant disability/incapacity or
5) A congenital anomaly of birth defect
6) Other important medical event. Infections resulting from contaminated study drugs will be considered a medically important event and subject to expedited reporting

An SAE may or may not be related to study drug.

10.3 Assessment of Causal Relationship of Adverse Events and Serious Adverse Events

The Investigator must separately determine the relationship of the event to the study drug. The causal association of an AE or SAE to study drug administration should be determined as follows: AEs or SAEs that are considered to have a definite, probable, or possible relationship to treatment with the study drug will be recorded as “related/suspected” while those that are considered to be unlikely or unrelated to treatment with the study drug will be recorded as “unrelated/not suspected”.

The causal relationship of an AE or SAE will be classified in two categories, suspected and not-suspected, according to the detailed criteria defined in Section 10.6. It is the responsibility of the Investigator to provide the causality analysis when recording an SAE Report; however, the Sponsor, through the pharmacovigilance service provider (Acumen Medical Information & Technology Co., Ltd., [AMIT]), may provide additional analysis and assessment while submitting the report to FDA following the local regulations.

10.4 Assessment of Severity of Adverse Events and Serious Adverse Events

The Investigator must determine the severity of each AE based on the grade in Common Terminology Criteria for Adverse Events (CTCAE)v5.0 (Table 10). Severity describes the intensity of the AE. Events that change severity during the course of follow up should be recorded on separate rows on the CRF, using the appropriate verbatim term but with the start date of each new event corresponding to the date that the severity increased or decreased.

Table 10. Assessment of Severity of an Adverse Event

Grade	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.5 Adverse Event and Serious Adverse Event Reporting

The AE reporting period starts with signing the ICF. Any AE collected before the first administration of study drug is considered not suspected or not related to the study drug, therefore will not be counted as a related AE in the final Clinical Study Report. Collection of AEs continues throughout the study.

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF. The SAE information will be recorded in the SAE Report Form provided by AMIT. It is not acceptable for the Investigator to send photocopies of the patient's medical records to AMIT in lieu of completion of the SAE Report Form/AE/SAE CRF page, unless such medical records are requested by AMIT for further understanding the AE/SAE cases. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

For each AE/SAE, the Investigator must document in the medical record that they have reviewed the AE/SAE and provided an assessment of causality. There may be situations in which an SAE occurs but the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the

Sponsor. The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

An AE or SAE is considered "unexpected" if it is not listed in the BSI-045B Investigator's Brochure or is not listed at the specificity or severity that has been observed. "Unexpected" as used in this definition also refers to AEs, SAEs, or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Patients in this study who experience an AE or SAE will be followed until the AE or SAE is resolved, has stabilized and is not expected to change, or is clearly determined to be due to a patient's stable or chronic condition or intercurrent illness, even if this occurs after the Termination Visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate CRF.

When a unifying diagnosis has been made that accounts for several possible signs and/or symptoms, the unifying diagnosis should be selected as the AE term. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as "upper respiratory syndrome" if this diagnosis has been made, rather than reporting the individual symptoms as separate events.

Safety and tolerability will be determined by symptoms, signs, and laboratory test abnormalities. The Investigator will monitor the laboratory test findings. If any laboratory test is abnormal during the course of the study, it will be followed at the discretion of the Investigator. Abnormalities of laboratory tests, in the opinion of the Investigator, may be considered of potential clinical concern and, thus, constitute a laboratory AE or be associated with a clinical AE. In such cases, they must be reported on the AE Form.

10.6 Procedures for Reporting Serious Adverse Events

All SAEs occurring during the course of the study, as defined by the protocol, regardless of the relationship to the study drug, must be reviewed and reported by the Investigator to the Sponsor through the contract research organization (CRO), AMIT, Floor 15, Building 14-2, Xingzhihui Business Garden, No. 19, Xinghuo Road, Jiangbei New District, Nanjing City, Jiangsu Province, China, within 24 h from the point in time when the Investigator becomes aware of the SAE.

The information collected by the Investigator will include at minimum the following: patient number, the criteria met for the AE being serious, the event term, date and time of onset, a narrative description of the event, and an assessment by the Investigator as to the severity of the event and relatedness to the study drug.

The Investigator is obligated to assess the relationship between study intervention and each AE/SAE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. The Investigator will also consult the BSI-045B Investigator's Brochure, or for marketed products, the product information, in making their assessment.

If the Investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the Sponsor in the protocol. In addition, if the Investigator determines that an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the SAE Report Form and in accordance with the SAE reporting requirements.

The Investigator will complete the SAE Report Form with their signature and date on each page of the report, scan it into a PDF file, and send the file to AMIT and the Sponsor through e-mail Biosion-RGPV@rg-pharma.com and submit to the local approving IRB within 24 hours of first awareness of this SAE. In case the Investigator has no access to e-mail, the signed SAE Report can be sent to AMIT via fax at the number 86-10-8801-9165 and be additionally shared with the Sponsor by AMIT.

The SAE Report will be further processed by AMIT into the pharmacovigilance database and submitted to FDA in case of serious, unexpected, and related AEs (suspected unexpected serious adverse reaction [SUSAR]) within 7 days of the day of first awareness for life-threatening or more severe cases, or 15 days of the day of first awareness for the cases at all other severity levels. The reports submitted to FDA will be forwarded to the study operation service CRO (ICON Clinical Research Limited [ICON]) through e-mail in the format of XML or MedWatch 2500A Form for the purpose of sharing with all the Investigators at the earliest availability. The information from all the SAEs will be forwarded to ICON periodically.

The Sponsor will promptly notify the Investigator about important safety or toxicology information as it becomes available. It is the responsibility of the Investigator to promptly notify the IRB about new and relevant safety information regarding the IP, including serious adverse drug reactions involving risk to human patients, in accordance with the applicable policies. The SAE reporting period is the same as the AE reporting period (starts with the signing of the ICF and continues through the termination visit).

The Sponsor will notify the FDA or all serious, unexpected, and related AEs within 15 calendar days after the study team receives knowledge of the event, and all life-threatening and/or fatal events within 7 calendar days after the study team receives knowledge of the event.

10.7 Follow-up of SAEs and AEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide AMIT with a copy of any postmortem findings including histopathology. New or updated information will be recorded in the originally completed CRF. The Investigator will submit any updated SAE data to the Sponsor, AMIT and IRB within 24 hours of receipt of the information. AMIT will further process the SAE in the same time frame as for the initial SAE Report.

10.8 Special Situations

Regardless of whether associated with an AE or SAE, special situation reports should be generated for all instances of medication error, abuse, misuse or overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the study drugs, product complaints, counterfeit of falsified medicine, and pregnancy, and forwarded to Sponsor through AMIT via e-mail or fax within one (1) working day.

10.9 Pregnancy Reporting

If a female study patient becomes pregnant during the study or within 90 days since the last dose, BSI-045B should be discontinued and the Sponsor notified within one working day using a Pregnancy Monitoring Form.

If the partner of a male patient becomes pregnant within 90 days since the last dose the Sponsor should be notified as soon as possible. Consent by the female partner of a male patient must be obtained prior to any data collection.

Pregnant patients or pregnant partners of male patients should be advised to inform their treating physician of their involvement in study BSI-045B-002.

All pregnancies must be followed up through delivery or other fetal outcome. An abnormal pregnancy outcome (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) is considered an SAE, reportable to the Sponsor within one working day.

11 STATISTICAL METHODS

11.1 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%.

11.2 Statistical Approach

Statistical analyses will be descriptive in nature, with frequencies and percentages generated for categorical variables and mean, standard deviation, median, minimum, and maximum values generated for continuous variables. Exact one-sided 95% confidence intervals will be generated for primary and select secondary efficacy endpoints based on proportions.

Additional details regarding the statistical analyses will be presented in the Statistical Analysis Plan.

11.3 Study Population

11.3.1 Patient Disposition

The number of patients screened, enrolled, and dosed from screening to the completion of the study will be listed, and the number and percentage of patients who have completed or withdrawn from the study by dose group will be presented.

Patients who discontinue treatment will be summarized and the primary reason for discontinuation. Patient disposition will be summarized.

11.3.2 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 patient’s rights, safety, or well-being. Important protocol deviations may result in the removal of patients from the study and the analysis.

Protocol deviations will be classified as important and non-important by the Sponsor and Investigators prior to database lock.

Protocol deviations will be summarized.

11.3.3 Baseline Characteristics

Baseline characteristics will be summarized descriptively, for demographic information, prior medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests. Baseline is defined as the most recent non-missing measurement prior to the patient receiving their first dose of study drug.

11.4 Efficacy Assessments

Statistical analysis of efficacy assessments includes changes in the EASI, IGA, and PP-NRS. Methods are described in detail in the SAP.

11.5 Safety Assessments

All AEs will be coded using the Medical Dictionary for Regulatory Activities. An AE (classified by preferred term) will be considered a TEAE if it was not present before the first dose of study drug or if it was present before the first dose of study drug but increased in severity during the assessment period for AEs. The incidence of TEAEs will be summarized by system organ class and preferred term. Multiple AEs mapped to the same preferred term will be counted once per patient.

Concomitant medications will be coded using The World Health Organization (WHO) Drug Dictionary with generic term and Anatomical Therapeutic Chemical (ATC) code and summarized by ATC code and WHODrug generic name. Safety laboratory findings, AEs, vital signs, and 12-lead ECGs will be summarized using descriptive statistics. Values and changes from baseline at scheduled time points will be summarized. Laboratory data will be listed and values and changes from baseline will be summarized.

11.6 Pharmacokinetic Data Analysis

Pharmacokinetics listings will be provided. Pharmacokinetic parameters will be estimated using NONMEM® Version 7.4 (or later versions) software with compartmental modeling analysis. Based on data availability, a PK/PD model will be developed to evaluate the relationships between serum BSI-045B and clinical efficacy.

11.6.1 Analysis of Serum Drug Concentration versus Time Data

The mean (and standard deviation) serum BSI-045B concentration-time profile in a semi-logarithmic scale for all patients will be plotted based on planned sampling time points. Individual concentration-time profiles in a semi-logarithmic scale for each patient will be plotted based on actual blood collection times.

11.7 Immunogenicity Analysis

The titers of ADA-positive patients will be listed, and the number, incidence, and 95% CI of patients 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.

11.8 Pharmacodynamic Biomarker Analysis

The biomarker levels of patients (values and percent changes from baseline) will be summarized by descriptive statistics.

12 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

12.1 Institutional Review Board

The protocol and ICF for this study must be reviewed and approved by an appropriate IRB before patients are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, GCP, and the Declaration of Helsinki. A letter, documenting the approval that specifically identifies the protocol by number and title as well as the Investigator, must be received by the Sponsor before initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

Upon the completion or termination of the study, the Investigator will notify the IRB.

12.2 Informed Consent

To obtain valid consent, each patient must be provided with written information describing the nature and duration of the study, the risks associated with the study, the burden on the patient and details of what will happen to any personal or health information collected. The patient must be provided with this information, given an opportunity to ask questions, and be given time to be able to consult with support persons or physicians such as a general practitioner. The patient must sign a written ICF indicating that they have read and understood the information sheet and what they are being asked to do. The ICF must be in a language in which the patient is fluent and must be signed before study-specific procedures are conducted. The signed and dated ICF will be retained with the study records.

12.3 Data Reporting and Case Report Forms

Data for each patient will be entered into the CRF and verified by the Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient's clinical status.

The Investigator or designated representative should complete the CRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. CRF data will be processed in a US 21 Code of Federal Regulations Part 11-compliant system.

12.4 Retention of Data

Regulations require that a copy of records (eg, laboratory data slips, source documents, test article disbursement records) that support case records of this study must be retained in the files of the responsible Investigator for a minimum of 15 years.

12.5 Deviations from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify the Sponsor's Medical Monitor and the IRB promptly regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. Any other changes or deviations in the protocol will be made as an amendment to the protocol and must be approved by the Sponsor and the IRB before the changes or deviations are implemented. The Sponsor will not assume any responsibility or liability for any deviation or change that is not described as part of an amendment to the protocol, or protocol clarification letters.

12.6 Study Monitoring

The Investigator will allow representatives of the Sponsor to periodically audit (at mutually convenient times before, during, and after the study has been completed) all CRFs and relevant portions of office, clinical, and laboratory records for each patient. Appropriate source documents, including documents that support patients' eligibility (eg, medical history, concomitant medications) should be made available to the Clinical Monitor. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of CRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

12.7 Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those approved by the Sponsor is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including FDA and the Sponsor and its agents will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patients' identities will remain confidential.

13 REFERENCES

Adbry® (tralokinumab-ldrm), for subcutaneous use [prescribing information]. Updated November 2022. https://www.adbryhcp.com/?gclid=Cj0KCQiAxbefBhDfARIsAL4XLRqFIlcbsQ_k9220a4XyVK8itsB8ssHsg0SOCVoBws_DKjHQimQy4dEaAjMDEALw_wcB. Accessed February 16, 2023.

Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. Expert Opin Ther Targets. 2020 Aug;24(8):777-792. doi: 10.1080/14728222.2020.1783242. Epub 2020 Jun 27. PMID: 32567399.

Han X, Krempski JW, Nadeau K. Advances and novel developments in mechanisms of allergic inflammation. Allergy. 2020 Dec;75(12):3100-3111. doi: 10.1111/all.14632. Epub 2020 Nov 4. PMID: 33068299.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatovener (Stockholm) Suppl. 1980: 92: 44-47. Available at: https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555924447. Accessed January 17, 2023.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8. doi: 10.1034/j.1600-0625.2001.100102. x. PMID: 11168575.

He R, Geha RS. Thymic stromal lymphopoietin. Ann N Y Acad Sci. 2010 Jan;1183:13-24. doi: 10.1111/j.1749-6632.2009.05128.x. PMID: 20146705; PMCID: PMC2895428.

Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020 Aug 1;396(10247):345-360. doi: 10.1016/S0140-6736(20)31286-1. Erratum in: Lancet. 2020 Sep 12;396(10253):758. PMID: 32738956.

Liu R, Zhang L, Qi L, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of a human monoclonal antibody TQC2731 targeting thymic stromal lymphopoietin in healthy adults: a first-in-human, randomized, placebo-controlled, double-blind, phase 1 study [abstract]. American Academy of Allergy Asthma and Immunology meeting 2023. Abstract 059.

Locksley RM. Asthma and allergic inflammation. Cell. 2010 Mar 19;140(6):777-83. doi: 10.1016/j.cell.2010.03.004. PMID: 20303868; PMCID: PMC3134388.

Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021 May 13;384(19):1800-1809. doi: 10.1056/NEJMoa2034975. PMID: 33979488.

Nakajima S, Kabata H, Kabashima K, Asano K. Anti-TSLP antibodies: Targeting a master regulator of type 2 immune responses. Allergol Int. 2020 Apr;69(2):197-203. doi: 10.1016/j.alit.2020.01.001. Epub 2020 Jan 21. PMID: 31974038.

National Eczema Association. Eczema Stats. Available at: https://nationaleczema.org/research/eczema-facts/. Accessed February 9, 2023.

Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI; ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009 Dec;124(6):1251-8.e23. doi: 10.1016/j.jaci.2009.10.009. PMID: 20004783.

Parnes JR, Sullivan JT, Chen L, Dias C. Pharmacokinetics, safety, and tolerability of tezepelumab (AMG 157) in healthy and atopic dermatitis adult subjects. Clin Pharmacol Ther. 2019 Aug;106(2):441-449. doi: 10.1002/cpt.1401. Epub 2019 Mar 23. PMID: 30779339; PMCID: PMC6766783.

Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1989; 144:13-4. doi: 10.2340/000155551441314. PMID: 2800895.

Sakamoto K, Matsuki S, Irie S, Uchida N, Hayashi N, Horiuchi M, Ren S. A Phase 1, randomized, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of subcutaneous tezepelumab in healthy Japanese men. Clin Pharmacol Drug Dev. 2020 Oct;9(7):833-840. doi: 10.1002/cpdd.775. Epub 2020 Jan 20. PMID: 31960624; PMCID: PMC7586988.

Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, van der Merwe R. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial. J Am Acad Dermatol. 2019 Apr;80(4):1013-1021. doi: 10.1016/j.jaad.2018.11.059. Epub 2018 Dec 12. PMID: 30550828.

Verstraete K, Peelman F, Braun H, et al. Structure and antagonism of the receptor complex mediated by human TSLP in allergy and asthma. Nat Commun. 2017 Apr 3;8:14937. doi: 10.1038/ncomms14937. PMID: 28368013; PMCID: PMC5382266.

Yang D, Han Z, Oppenheim JJ. Alarmins and immunity. Immunol Rev. 2017 Nov;280(1):41-56. doi: 10.1111/imr.12577. PMID: 29027222; PMCID: PMC5699517.

Wilson SR, Thé L, Batia LM, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. Cell. 2013 Oct 10;155(2):285-95. doi: 10.1016/j.cell.2013.08.057. Epub 2013 Oct 3. PMID: 24094650; PMCID: PMC4041105.

Zheng Y, Abuqayyas L, Megally A, Fuhr R, Sałapa K, Downie J, Colice G. Tezepelumab pharmacokinetics, safety, and tolerability after administration via vial-and-syringe, accessorized prefilled syringe, or autoinjector: a randomized trial in healthy volunteers. Clin Ther. 2021 Jan;43(1):142-155.e5. doi: 10.1016/j.clinthera.2020.11.014. Epub 2020 Dec 27. PMID: 33380362.

Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). Adv Pharmacol. 2013;66:129-55. doi: 10.1016/B978-0-12-404717-4.00004-4. PMID: 23433457; PMCID: PMC4169878.