Clinical Trial Protocol

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of GBR 830 in Adult Subjects With Moderate to Severe Atopic Dermatitis

Protocol Number: GBR 830-204, Version 10.0, Amendment 9

Dated: 05-May-2020

ClinicalTrials.gov Identifier: NCT03568162

EudraCT Number: 2018-000783-29

Sponsor: Ichnos Sciences SA

ISB 830

GBR 830-204

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF GBR 830 IN ADULT SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Phase of Development	Phase 2b
Sponsor	Ichnos Sciences SA [redacted]
Protocol Number	GBR 830-204
IND Number	126820
EudraCT Number	2018-000783-29
Approved by	[redacted]
Protocol Version	Version 10.0, Amendment 9
Date	05-May-2020
Supersedes	Version 9.0, Amendment 8

This study must be conducted in accordance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigational Brochure (IB) for GBR 830/ISB 830. I have read the GBR 830-204 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR'S SIGNATURE

This protocol reflects the Sponsor's current knowledge of ISB 830 as applicable to this study. It has been designed to achieve the stated objectives while minimizing exposure to, and risk from, both the products being used and the assessments. The assessments are all considered to be appropriate, capable of validating the stated objectives of the study, and of providing the necessary information to ensure subject safety. The protocol has been designed according to the principles of the ICH guidelines for GCP, and the Declaration of Helsinki. It has undergone both medical and scientific review by the Sponsor. The Sponsor is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the electronic case report forms (eCRFs).

- We hereby agree to conduct the study in accordance with this protocol and the above-mentioned guidance/ regulation.
- We agree to comply with all relevant standard operating procedures (SOP) required for the conduct of this study.
- We further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

Signed on behalf of the Sponsor, Ichnos Sciences SA:

Clinical Lead:

[redacted] Date:

Reviewed and Approved by:

[redacted] Date:

2. SYNOPSIS

Name of Sponsor/Company: Ichnos Sciences SA	
Name of Study Drug: ISB 830	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of GBR 830 in Adult Subjects with Moderate to Severe Atopic Dermatitis	
IND no: 126820	**EudraCT no:** 2018-000783-29
Phase of development: 2b	
Indication: Moderate to Severe Atopic Dermatitis	

Objectives:

Primary:

- To characterize the efficacy of ISB 830 monotherapy in adults with moderate-to-severe atopic dermatitis (AD) compared to placebo as measured by percentage change from baseline in Eczema Area and Severity Index (EASI) score at Week 16.

Secondary:

- To evaluate safety, tolerability, pharmacokinetics (PK), and immunogenicity of ISB 830 in adults with moderate-to-severe AD.
- To measure the effect of ISB 830 on disease activity in adult subjects with moderate-to-severe AD, as measured by validated tools (such as Investigator's Global Assessment [IGA], EASI response, SCORing Atopic Dermatitis [SCORAD]).

Exploratory:

- To evaluate pharmacodynamics (PD) of ISB 830 in adults with moderate-to-severe AD.

Study population:

Adult males and females (≥18 years of age) with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks in the opinion of the Investigator).

Moderate-to-severe AD is defined by an IGA score of 3 or higher at screening and baseline, consistent with the categories of moderate (IGA=3) and severe (IGA=4); and an EASI score of 12 or higher at screening or 16 or higher at baseline.

Study design:

This is a multicenter, double-blind, placebo-controlled study. The study will be conducted in 4 phases: a screening phase, a blinded treatment phase, an open-label treatment phase, and a follow-up phase. Subjects will participate in a 54-week treatment period (including 52 weeks of study drug administration) with 12 weeks follow-up at end of the treatment phase from Week 54 to Week 66. The study will be conducted in 2 Parts, with dosing Groups 1-4 comprising Part 1, and dosing Groups 5-6 comprising Part 2.

The blinded treatment phase consists of a randomized, placebo-controlled treatment with ISB 830 for 16 weeks at different dose levels (see below). The open-label treatment phase consists of a 38-week treatment phase where ISB 830 will be administered every other week (q2w) subcutaneously (SC). The primary endpoint of the study will be assessed at the end of the blinded treatment period at Week 16.

Subject eligibility will be assessed during screening, which will occur within 28 days prior to randomization. During the screening period, treatments for AD will be withdrawn or modified for the subject as defined in the protocol (Table 5). Subjects may be re-screened once (within or outside of the screening period) if they fail the screening evaluation. All screening procedures will be repeated during rescreening.

Subjects who continue to meet eligibility criteria will undergo Day 1/baseline (predose) assessments and will be randomized to equal groups of approximately 78 subjects each.

Subjects will receive SC injections of ISB 830, or corresponding placebo. A total of 27 doses (ISB 830 or placebo) will be administered q2w.

During the blinded treatment phase each subject will receive a dose on Day 1 and q2w starting from Day 15 through Week 14, according to the following treatment assignment and table below:

Study Part 1:

- Group 1: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume), starting at Day 15 (Week 2).
- Group 2: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by dosing every 4 weeks (q4w) of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted]) will be administered q4w starting at Day 15 (Week 2).
- Group 3: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q4w dosing of 75 mg ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted] will be administered q4w starting at Day 15 (Week 2).
- Group 4: Dose of placebo (2 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (1 SC injection of [redacted]) starting at Day 15 (Week 2).

Study Part 2:

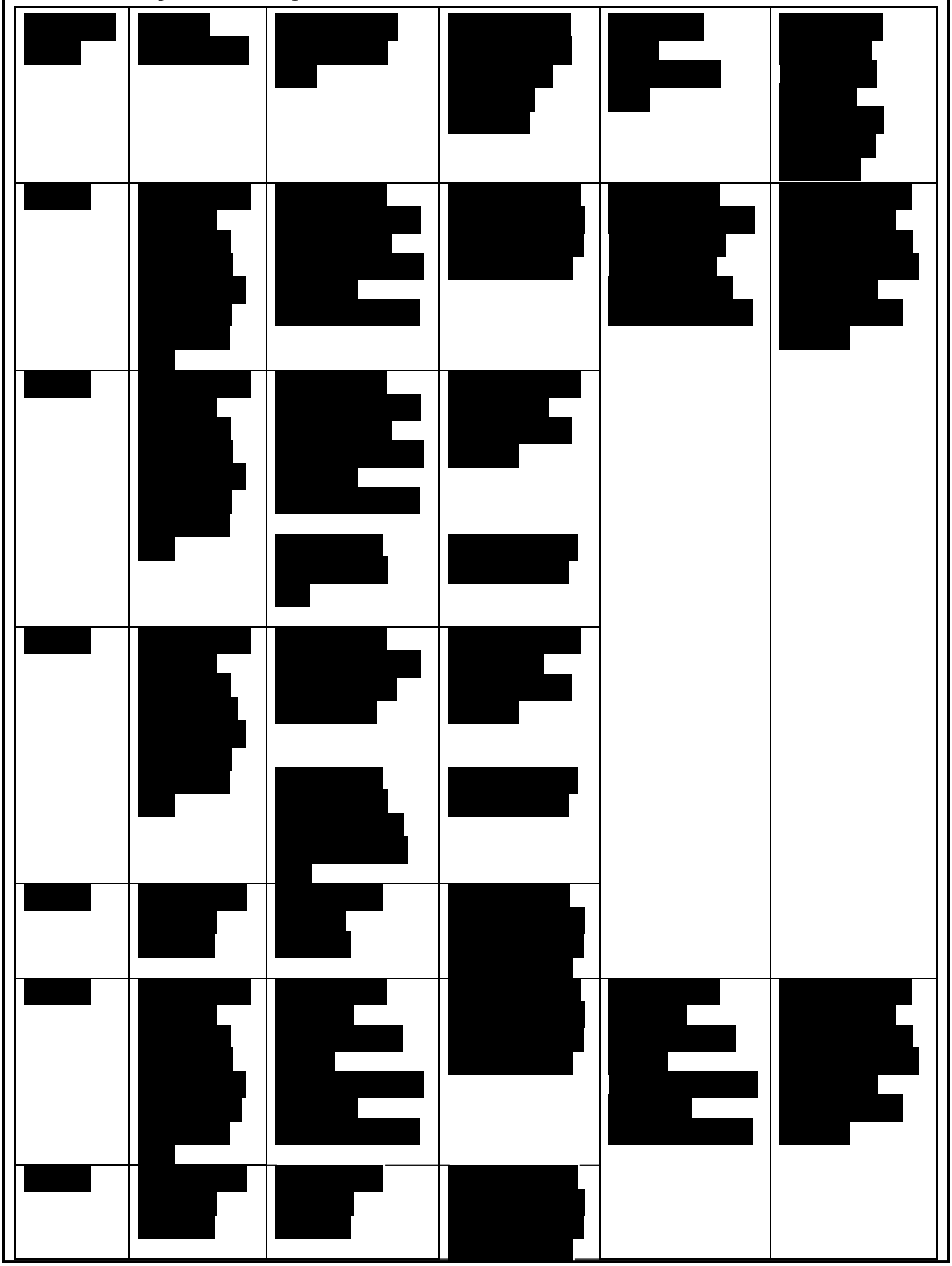
- Group 5: [redacted] ISB 830 (4 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (2 SC injections containing [redacted] volume), starting at Day 15 (Week 2).
- Group 6: Dose of placebo (4 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (2 SC injections of [redacted] starting at Day 15 (Week 2).

During the blinded treatment phase all subjects in Groups 1 through 4 will receive a loading dose consisting of 2 SC injections, followed by 7 maintenance doses consisting of 1 SC injection per dose. For Groups 5 and 6, all subjects will receive a loading dose consisting of 4 SC injections, followed by 7 maintenance doses consisting of 2 SC injections per dose, as described above and in protocol Section 10.1, Table 6.

During the open-label treatment phase each subject will receive 19 doses of ISB 830 SC injection [redacted]) q2w (consisting of 1 to 2 SC injections per dose, respectively) from Week 16 to Week 52 or until subject withdrawal, as described above and in protocol Section 10.1, Table 6.

All subjects in Groups 1-4 in the open-label treatment phase will receive [redacted] q2w. All subjects in Groups 5-6 in the open-label treatment phase will receive [redacted] q2w.

Treatment Groups and Dose Regimens



Safety assessments, clinical laboratory assessments, vital sign assessments, PK sampling, immunogenicity sampling, and clinical efficacy assessments (IGA and EASI) will be performed by the blinded Investigator and blinded study staff as defined in Table 2 of the protocol (Schedule of Assessments), or until the subject discontinues from the study.

An experimental population PK design will be used for the PK blood sampling. The subjects in the rich PK group will have additional blood sampling between Days 1 to 8 (Week 1), and Days 85 to 92 (Week 12) compared to the sparse PK group. The subjects in the sparse PK group will have widespread sampling with fewer time points for each subject (compared to the rich PK group). Approximately 80 rich PK subjects will be randomized (in a 1:1:1:1 ratio) to treatment groups 1-4 and approximately 40 rich PK subjects will be randomized (in a 1:1 ratio) to treatment groups 5 and 6. The remaining subjects in the study will be included in the sparse PK group. Blood samples will be collected from the rich and sparse PK subjects according to the respective schedule described in Table 8 of the protocol.

End-of-treatment (EOT) visits will be conducted on Day 113 (Week 16) for the blinded treatment phase and at Day 379 (Week 54) for the open-label treatment phase for all subjects. Subjects should continue into the follow-up period and will have a follow-up phone call 4 and 8 weeks after the last EOT visit [Day 407 (Week 58) and Day 435 (Week 62) respectively] and a final clinic visit 12 weeks after the EOT [Day 463 (Week 66)] visit.

Subjects who withdraw consent from the blinded treatment phase prior to Week 16 will undergo the blinded treatment phase EOT visit procedures and enter the follow-up period.

Subjects who withdraw consent from open-label treatment phase prior to Week 52 will undergo the open-label treatment phase EOT visit procedures and enter the follow-up period.

All subjects continuing in the follow-up period will have a follow-up phone call 4 and 8 weeks after the last EOT visit and a final clinic visit 12 weeks after the EOT visit as described in the Table 3 follow-up period.

Subjects will be clinically monitored for safety throughout the study, including anaphylactic reactions and/or injection site reactions (ISRs), with monitoring at the study site for 2 hours after the first dose on Day 1 (in the blinded treatment phase) and on Day 113 (Week 16) (first dose in open-label treatment phase) and for 1 hour after dosing at all other visits.

To allow subjects access to the open-label treatment phase of the study, subjects who have completed the GBR 830-204 study prior to implementation of the protocol amendment that includes the open-label phase (eg, Protocol Amendment 3 (version 4.0) and/or Amendment 6 (version 7.0)) or who are in the follow-up phase of the study at the time of implementation of the open-label protocol amendment, may be eligible to participate in the open-label treatment phase of this study. Subjects who have completed the study prior to implementation of the open-label protocol amendment must undergo a modified Screening visit (as per Table 2 of the protocol), and if eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1and 5), will undergo study assessments as per Table 3 of the protocol. Subjects who are in the follow-up period of GBR 830-204 at the time the open-label protocol amendment is implemented must complete their follow-up period as per protocol, and then must undergo a modified Screening visit (as per Table 2 of the protocol), and if eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1 and 5), will undergo study assessments as per Table 3 of the protocol. This includes a complete washout of any concomitant medications and therapies received (as per Table 5 of the protocol) prior to starting the open-label treatment phase of the study.

Study endpoints:

Primary Endpoint:

- Percentage change from baseline in EASI score at Week 16.

Secondary Endpoints:

Efficacy Endpoints:

- Proportion of subjects with EASI-75 (≥75% improvement from baseline) at Week 16.
- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points at Week 16.

- Proportion of subjects with improvement (reduction) of Pruritus Numerical Rating Scale (NRS) ≥4 from baseline to Week 16.
- Proportion of subjects who achieve an EASI 50 (≥50% improvement from baseline) response from baseline through Week 16.
- Change in SCORAD from baseline through Week 16.
- Change in the Dermatology Life Quality Index (DLQI) from baseline through Week 16.
- Change in Global Individual Signs Score (GISS) (erythema, infiltration/papulation, excoriations, lichenification) from baseline through Week 16.
- Change in Hospital Anxiety Depression Scale (HADS) from baseline through Week 16.
- Change in Patient Oriented Eczema Measure (POEM) from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Disease from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Treatment from baseline through Week 16.
- Assessment of sick leave and/or missed school days through Week 16.

Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through Week 16 and Week 54.
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of conjunctivitis TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through Week 16 and Week 54.
- Incidence of TEAEs leading to treatment discontinuation from baseline through Week 16 and Week 54.
- Overall number of TEAEs and SAEs through Week 16 and Week 54.
- Vital signs, clinical laboratory values, and electrocardiogram (ECG) results monitored from baseline through Week 16 and Week 54.
- Formation of anti-drug antibodies (ADA) to ISB 830 to evaluate immunogenicity.

Pharmacokinetics Endpoints:

- C_{max}, t_{max}, AUC_{tau}, AUC_{0-t}, and other related parameters will be estimated using data from the rich PK group from the blinded treatment phase. C_{trough} values will be estimated using data from both rich and sparse PK groups from the blinded treatment phase.

Exploratory Endpoints:

Samples for exploratory biomarker endpoints will be collected when and where biomarker sample kits are available.

Exploratory biomarker endpoints are:

- Messenger RNA (mRNA) expression of immune and barrier measures in skin biopsies at baseline, end of Week 8, and end of Week 16.
- Biomarker analysis in ISB 830 responder and non-responder populations to evaluate the relationship of biomarkers with clinical efficacy measures.
- Assays on plasma, serum, viably frozen peripheral blood mononuclear cells (vfPBMCs) and/or cell subsets/derivatives.

Exploratory efficacy endpoints are:

- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points through Week 54.
- Proportion of subjects with EASI-75 (≥75% improvement from baseline) through Week 54.
- Proportion of subjects who achieve an EASI-50 (≥50% improvement from baseline) through Week 54.
- Change in the European Quality of Life Status (EQ-5D) through Week 16.
- Change in Juniper Asthma Control Questionnaire (ACQ-5) from baseline through Week 16.
- Change in the Sino-nasal Outcome Test (SNOT-22) from baseline through Week 16.
- To assess qualitative changes in photographs of skin lesions taken at time points specified in the Schedule of Assessment.

Number of subjects (planned):

For Groups 1 through 4, a sufficient number of subjects will be screened to randomize approximately 312 eligible subjects in a 1:1:1:1 ratio. For Groups 5 and 6, a sufficient number of subjects will be screened to randomize approximately 156 eligible subjects in a 1:1 ratio to either ISB 830 or placebo, therefore approximately 468 subjects are planned to be randomized in this study. The randomization will be stratified by disease severity (moderate or severe, as assessed by IGA), geographic region (North America vs European Union), and subjects consenting to rich PK sampling (Yes/No). The actual number of subjects randomized in Groups 5 and 6 may be different than initially planned due to the impact of the SARS-CoV-2/COVID-19 pandemic (see Section 8.3.4).

Main criteria for inclusion:

1. Provided written informed consent and any locally required authorization prior to any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with all aspects of the protocol.
3. Male or female ≥18 years at the time of screening.
4. Physician diagnosis of AD for > 1 year; diagnosis of AD as defined by the American Academy of Dermatology Consensus Criteria (Eichenfeld et al, 2014).
5. AD involvement of ≥10% Body surface area (BSA) at screening and baseline.
6. EASI score of ≥12 at screening or ≥16 at baseline.
7. IGA score of ≥3 at screening and baseline (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe).
8. Baseline Pruritus NRS score for maximum itch intensity ≥3 over the previous 24 hours. A minimum of 3 days of diary completion is required in the week prior to randomization.
9. Documented/reported recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications (topical corticosteroids or crisaborole or topical calcineurin inhibitors) or subjects for whom topical treatments are otherwise medically inadvisable (eg, because of

important side effects or safety risks as defined in the protocol). Documents may include medical records, physician to healthcare provider communication (with date and time of communication and physician signature), or, pharmacy records (with clearly listed dates of dispensation). A course of marketed systemic immunosuppressants (eg, prednisone, cyclosporine, and methotrexate) for AD in the 6 months prior to screening assumes failure of topicals and is acceptable in place of topical failure.

10. Have applied a stable dose of topical emollient (moisturizer) twice-daily for at least 7 consecutive days immediately before the baseline visit (with the exception of prohibited moisturizers containing additives listed in Exclusion Criteria #5).
11. Must agree to the following requirements during the study:
    a. If female and of childbearing potential, she must have a negative serum pregnancy test result within 7 days prior to first dosing and a negative urine pregnancy test predose on Day 1. She must be willing to use a highly effective form of contraception (ICH E8 Guideline, 1997; (ICH M3 [R2] Guidance, 2009; (FDA M3 [R2] Guidance, 2010) for the duration of the study and for at least 3 months after the last dose of study medication. Methods like periodic abstinence, post ovulation procedures and withdrawal are not considered adequate. Each woman will be considered to have childbearing potential unless she has been surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy or has been post-menopausal for at least 2 years. For postmenopausal women only, follicle stimulating hormone (FSH) testing will be performed at screening to confirm non-childbearing potential (FSH ≥40 IU/L).
    b. If male with a partner of childbearing potential, he must be willing to use condoms in combination with a second effective method of contraception during the study. Each man will be considered as potent unless surgically sterilized (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate). Male subjects must continue to use contraception for 180 days following administration of the study drug.
    c. Male subjects should agree not to donate sperm during the study and for 180 days following administration of the study drug.

Main criteria for exclusion:

1. Prior treatment with ISB 830.
2. Employee of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
3. Concurrent enrollment in another investigational clinical study.
4. Treatment with any of the following before baseline:
    a. Investigational biological agent within 8 weeks of baseline or 5 half-lives, whichever is longer.
    b. Investigational drugs eg, phosphodiesterase type 4 (PDE4) inhibitors, Janus kinase (JAK) inhibitors, within 4 weeks of baseline.
    c. Phototherapy for AD within 4 weeks of baseline.
    d. Marketed drugs, including systemic corticosteroids, immunosuppressive/immunomodulatory drugs including but not limited to cyclosporine, mycophenolate mofetil, interferon-gamma (IFN-γ), PDE4 inhibitors, JAK inhibitors, azathioprine or methotrexate within 4 weeks of baseline.
    e. Topical medications, including corticosteroids, tacrolimus, and/or pimecrolimus, and crisaborole within 1 week of baseline.
    f. Regular use (>2 visits/week) of a tanning booth/parlor within 4 weeks of baseline.
    g. Biologics, depending on the type of biologic such as cell-depleting agents including but not limited to rituximab: within 6 months of baseline, or until lymphocyte and CD19+ lymphocyte count returns to normal, whichever is longer.
    h. Biologics including infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, etanercept, anakinra, dupilumab: within 12 weeks of baseline, or 5 half-lives, whichever is longer.
    i. Other biologics: within 5 half-lives (if known).
5. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (subjects may continue using stable doses of such moisturizers if initiated before the screening visit).

6. Planned or anticipated use of any prohibited medications and procedures during study treatment as defined in the study protocol.
7. Subjects who are immunocompromised (congenital or acquired), or who have had a recent (within 3 months prior to baseline) or current serious systemic infection (including infectious mononucleosis-like illness or herpes zoster).
8. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit.
9. Subjects who have evidence of active or latent tuberculosis (TB) as documented in their medical history or test positive at screening. For indeterminate cases, an informed decision will be made between the Principal Investigator and Medical Monitor.
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: subjects may be rescreened after infection resolves.
11. Presence of skin comorbidities that may interfere with study assessments, in the opinion of the Investigator, including subjects with psoriasis.
12. Poorly controlled asthma as assessed by the Asthma Control Questionnaire [ACQ] based on International ERS/ATS guidelines.
13. Any condition at baseline which is part of the criteria for discontinuation of study drug as defined in the study protocol.
14. Subjects who are known to be seropositive for human immunodeficiency virus (HIV) or who test positive at screening.
15. History of a positive result for Hepatitis B surface antigen (HBsAg), antibody to Hepatitis B core antigen (anti-HBcAg), or antibody to Hepatitis C virus (anti-HCV) or presence of these findings at screening.
16. History of alcohol or drug abuse within 2 years of the screening visit.
17. Subjects with a history of non-malignant lymphoproliferative disorders, or a history of malignancy within 5 years before baseline (except completely treated in situ cervical carcinoma or non-metastatic squamous or basal cell carcinoma of the skin).
18. In the opinion of the Investigator, subjects with any other medical or psychological condition as well as laboratory values, which are significantly different from normal reference ranges and/or judged to be clinically significant; and/or any condition that would interfere with evaluation of the study drug or interpretation of subject safety or study results, including conditions that are inadequately understood at the time of screening.
19. Subjects with a history of substance abuse or dependence that in the opinion of the Investigator, is considered to interfere with the subject's participation in the study.
20. Planned or anticipated major surgical procedure during the subject's participation in this study.
21. Women who are pregnant or breast feeding.
22. Known hypersensitivity to monoclonal antibodies or any of the excipients of the drug product.

Estimated Duration of subject participation:

The anticipated maximum total study duration for each subject is approximately 70 weeks. This duration will consist of the screening period of up to 4 weeks, the blinded treatment period of up to 16 weeks (14 weeks of treatment, with a loading dose on Day 1 followed by maintenance dosing from Day 15 [Week 2] until the last dose at Week 14), the open-label treatment period of up to 38 weeks, and the follow-up period of 12 weeks starting at the end of the open-label treatment period. Subjects who consent to participate in the open-label treatment phase of the study after they completed the GBR 830-204 study, and require a modified screening visit, would have a study participation duration of up to 86 weeks.

Duration of treatment:

There is a 54-week treatment period (consisting of 52 weeks of dosing, including a blinded loading dose on Day 1 followed by blinded maintenance dose from Week 2 until Week 14, followed by open-label treatment dose from Week 16 to Week 52).

Investigational product, dosage and mode of administration:

Name of Investigational Product: ISB 830

Dosage Form: [redacted]

Dosage for blinded treatment phase: See Groups 1, 2, 3, and 5 in the Treatment Groups and Dose Regimens table, in the Study Design section above.

Dosage for open-label treatment phase: All subjects in Groups 1-4 in the open-label treatment phase will receive [redacted] of ISB 830 q2w. All subjects in Groups 5-6 in the open-label treatment phase will receive [redacted] q2w.

Mode of Administration: SC injection

Placebo therapy, dosage and mode of administration:

Placebo/Control: Placebo for ISB 830

Dosage Form: [redacted]

Dosage for blinded treatment phase: See Groups 2, 3, 4 and 6 in the Treatment Groups and Dose Regimens table, in the Study Design section above.

Dosage for open-label treatment phase: Not applicable.

Mode of Administration: SC injection

Criteria for evaluation:

Efficacy Assessments:

- The EASI is a validated measure used in clinical practice and clinical studies to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head/neck, trunk (including genital area), upper limbs, and lower limbs (including buttocks), and converted to a score of 0 to 6 (Hanifin et al, 2001).
- The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe).
- The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and intensity of AD. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The intensity of 6 specific symptoms of AD is assessed using the following scale: absence (0), mild (1), moderate (2), or severe (3), (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of pruritus and sleep-loss is recorded for each symptom by the subject or relative on a visual analogue scale (VAS), where 0 is no pruritus (or sleep-loss) and 10 is the worst imaginable pruritus (or sleep-loss), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C (Kunz et al, 1997).
- Pruritus Numerical Rating Scale (NRS): Subjects will respond to the following question, "On a scale of 0 – 10, with 0 being no itch and 10 being the worst itch imaginable, how would you rate your worst degree of itch during the previous 24 hours?" The Pruritus NRS will be assessed by the subject once per day in the morning, ideally at the same time; recorded by the subject after each assessment, and reviewed by study staff at each clinic visit.
- DLQI: The DLQI is a subject-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work, and school and personal relationships and treatment. Response categories include "a little," "a lot," and "very much" with corresponding scores of 1, 2, and 3, respectively; "not at all," "not relevant" responses

are scored as "0." Totals range from 0 to 30 (ie, from less to more impairment), and a 5 point change from baseline is considered clinically relevant (Finlay and Khan, 1994; Basra et al, 2008).

- GISS: Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria.
- Body Surface Area Involvement of Atopic Dermatitis (BSA): Body surface area affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.
- HADS: The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond and Snaith, 1983; Herrmann, 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.
- POEM: The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman et al, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.
- EQ-5D: The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3).
- ACQ-5: The ACQ-5 is a 5-question version of the Juniper ACQ and is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of subjects with a medical history of asthma.
- SNOT-22: The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life. The questionnaire will be administered only to a subset of subjects (eg, with chronic rhinitis/ rhinosinusitis, nasal polyps, allergic rhinitis).
- Patient Global Assessment of Disease: Subjects will rate their overall well-being based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent."
- Patient Global Assessment of Treatment: Subjects will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent."
- Assessment of Sick Leave and/or Missed School Days: Subjects who are employed or enrolled in school will be asked to report the number of sick leave and/or missed school days due to atopic dermatitis (eg, vs due to an accident) in the last 4 weeks.

Pharmacokinetic Assessments:

Blood samples will be collected from both rich and sparse PK groups at appropriate time points defined in Tables 2 and 3, and Table 8 in the protocol.

The serum concentrations of ISB 830 in these samples will be quantified using a validated enzyme-linked immunosorbent assay (ELISA) method. Serum concentration data from both rich PK and sparse PK group from the blinded treatment phase will be used to derive PK parameters, as appropriate.

Immunogenicity Assessments:

Blood samples will be collected at appropriate time points defined in Tables 2 and 3, and Table 8 in the protocol to detect the presence of anti-drug antibodies (ADA) to ISB 830, as per procedures similar to collection of PK samples. The presence or absence of ADA in these samples will be determined using a validated Electrochemiluminescence immunoassay (ECLIA) method.

Pharmacodynamic (Biomarker) Assessments:

Blood samples, including plasma, serum, whole blood, viably frozen peripheral blood mononuclear cells (vfPBMCs) and/or cell subsets will be collected from subjects randomized in the study at appropriate time points as defined in Table 2 and Table 8 in the protocol. Biomarker assessments to be performed on collected samples may include but not limited to:

- Leukocyte sub-population cell counts by flow cytometry
- Cytokines
- Biomarker in peripheral blood
- Total immunoglobulin E (IgE)
- Serum soluble OX40 ligand (OX40L) and serum soluble OX40
- Epigenetics

Exploratory Photographs:

Subjects, who agree to participate in the main study, also agree to allow photography of their skin (excluding pictures of the subject's face) during study participation at specified time points as per Table 2 and Table 3. Photographs of the subject's skin (with the exception of the face) may also be taken at additional time points, as per investigator judgment.

The photographs may be used to examine disease activity, autoimmunity/inflammation, ISB 830 mechanism of action, and/or the effect of the study drug(s) on the course of disease.

Details of photograph collection, processing, shipping and storage will be provided to the study sites in a separate manual.

Optional Genetic Research/Pharmacogenomics Assessments:

Subjects who provide written consent for Optional Genetic Research agree to provide a blood sample (one sample may be collected at any visit during the study) to evaluate genetic sequences that may be involved in disease activity, inflammation, study drug mechanism of action, PK/metabolism, and/or the effect of the study drug(s) on the course of disease. Subjects may decline this optional research without effect on their participation in the main study.

Safety Assessments:

Safety and tolerability of ISB 830 will be assessed based on adverse events (AEs), including anaphylactic events and ISRs; SAEs; vital signs; physical examinations; ECGs; and clinical laboratory parameters.

Subjects will be clinically monitored for safety throughout the study, including anaphylactic reactions and/or ISRs, with special monitoring at the study site for 2 hours after the first dose on Day 1 (in the blinded treatment phase) and on Day 113 (Week 16) (first dose in open-label treatment phase) and for 1 hour after dosing at all other visits.

Guidance will be given to the investigator for the criteria to be used to assess anaphylaxis (Sampson et al, 2006). Injection site reactions will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 that was published 14-Jun-2010 by the US Department of Health and Human Services (National Institutes of Health [NIH] and National Cancer Institute [NCI]).

Pandemic Related Safety Assessments:

To ensure the ongoing safety of subjects during the pandemic, study subjects who miss or are unable to attend scheduled clinic visits will be contacted by the site via a safety phone call that includes the collection of AEs/SAEs and concomitant medications. This phone call is to be performed for every missed visit that occurs during the pandemic. If the subject meets other criteria, eg, for withdrawal/discontinuation of the study drug, the site is to follow the protocol in regard to those criteria.

STATISTICAL METHODS:

For both Part 1 and Part 2 of the study, the primary endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM). The model will adjust for study treatment, baseline, randomization stratification factors, visit as well as baseline-by-visit and treatment-by-visit interactions.

The continuous secondary endpoints will be analyzed using the MMRM model as performed for the primary endpoint.

The Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity) will be used to analyze the categorical secondary endpoints.

For Part 2 of the study, Group 5 [redacted] will be compared to the corresponding placebo arm (Group 6) using the same statistical method used in the analysis of the first part of the study.

To assess the robustness of the results in the Part 2 of the study, the analyses on primary endpoint and secondary endpoints (IGA, EASI-75) will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

Parts 1 and 2 are two independent parts of the study protocol and will therefore be analyzed separately. That is, upon completion of the double-blind period of Part 1, the database will be partially locked. The data will be analyzed and the topline results (TLR) determined. Similar activities will take place upon the completion of the double-blind period of Part 2.

The efficacy results from these 2 parts of the study will be kept separate. However, the safety results will be presented side by side.

Details of efficacy, safety and PK analyses will be specified in the Statistical Analysis Plan (SAP) and included in the Clinical Study Report (CSR). Population pharmacokinetic and exposure-response modeling will be described in a Modeling Plan and data will be published in a separate report.

Biomarker analyses will not be part of the CSR and will be described separately.

Study Populations:

Full Analysis Set:

The Full Analysis Set (FAS) consists of all subjects who are randomized and received at least 1 dose of study medication. Based on the intent-to-treat principle, subjects will be analyzed according to the treatment group assigned.

Per Protocol Set:

The Per Protocol Set (PPS) consists of all FAS subjects who have no major protocol deviations of eligibility or on-treatment study conduct.

Safety Analysis Set:

The Safety Analysis Set (SAS) consists of all subjects who were randomized and took at least 1 dose of study medication. Subjects will be analyzed according to the treatment they received.

Pharmacokinetic Analysis Set:

The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAS population who received ISB 830 and for whom sufficient serum concentration data are available to facilitate derivation of PK parameters, do not have any major protocol deviation, and for whom the time of dosing and the time of sampling are known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time points from the PKAS will be documented in the SAP.

Determination of Sample Size:

[redacted]

Efficacy Analyses:

The primary efficacy analysis will be the percentage change from baseline in EASI score, and the secondary efficacy analysis will be the IGA and EASI 75 (subjects achieving 75% reduction from baseline in EASI score). The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The EASI and IGA scores will be assessed at time points described in the Schedule of Assessments.

To test the robustness of the MMRM for the primary endpoint, sensitivity analyses using the tipping point approach will be conducted. In addition, the primary endpoint will be analyzed using the complete dataset (subjects who complete the week 16 and had EASI measurements).

Detailed statistical methods, including methods for the multiplicity adjustment, the handling of missing data for the analysis of the primary as well as secondary and exploratory endpoints and the exploratory analyses on biomarkers will be described in the SAP and the Biomarker Analyses Plan.

Pharmacokinetic Analyses:

The PKAS will be used for the PK analyses. Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, and other related parameters) will be estimated using data from the rich PK group from the blinded treatment phase. Estimates of C_{trough} will be derived using the data from both rich PK group and sparse PK group from the blinded treatment phase. The PK parameters will be summarized in tabular and graphic form. Details of the PK analysis will be specified in the SAP.

The serum concentration data from both rich and sparse PK group may be used for the population PK analysis and will be reported separately.

Immunogenicity Analyses:

The number and percent incidence of positive and negative ADA status of subjects by treatment, and time points will be provided. Titers and neutralizing potential of confirmed positive samples will be reported. Details will be provided in the SAP.

Pharmacodynamic (Biomarker) Analyses:

Summary statistics will be provided for PD biomarkers.

Biomarker analyses will not be part of the CSR and will be described separately.

Safety Analyses:

Adverse events will be summarized by system organ class and preferred term. Subjects will be counted only once for each preferred term, system organ class, and by the highest severity of an event. Laboratory evaluations will be summarized with descriptive statistics at each visit, and change from baseline summarized for each post-baseline visit. Laboratory measurements will also be summarized based on the number and percentage of subjects above or below a pre-specified threshold for each test. AEs will be coded using MedDRA. Details will be presented in the GBR 830-204 SAP.

Data Safety Monitoring Board:

This study will institute a data safety monitoring board (DSMB) which will function independently of all other individuals associated with the conduct of this clinical study, including the site investigators participating in the study. The DSMB will be constituted prior to the randomization of the first subject. The DSMB will monitor subject safety by formally reviewing accumulated safety data by treatment group three times during the study. This includes but does not limit the role of the DSMB to evaluate these data and to provide recommendations to the sponsor to continue or modify the follow-up phase of the study as outlined in the DSMB charter.

It is expected that the DSMB will consist at a minimum of 2 physicians with appropriate disease area qualifications and 1 statistician. There will be a meeting with the DSMB describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DSMB charter.

Interim analyses:

No interim analyses are planned.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACQ-5	Asthma Control Questionnaire-5
AD	Atopic dermatitis
ADA	Anti-drug antibody (ies)
AE	Adverse event
ALT	Alanine aminotransferase
anti-HCV	Antibody to hepatitis C virus
AUC	Area under the curve
AUC0-∞	Area under the curve from time 0 to infinity
AUC0-t	Area under the curve from time 0 to the last measurable concentration
AUC0-tau	Area under the curve over dosing interval
BMI	Body mass index
BSA	Body surface area
Cmax	Maximum observed plasma concentration
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Serum concentration at end of dosing interval
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
ECLIA	Electrochemiluminescence immunoassay
ELISA	Enzyme-linked immunosorbent assay
EQ-5D	EuroQol-5D
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
GISS	Global Individual Signs Score
GvHD	Graft versus host disease
HADS	Hospital Anxiety Depression Scale
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigational Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IgG1	Immunoglobulin G1
IgE	Immunoglobulin E
IP	Investigational product
IRB	Institutional Review Board
ISRs	Injection Site Reactions
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JAK	Janus kinase
LAR	Legally acceptable representative
LLN	Lower limit of normal
MMRM	Mixed-effect Model for Repeated Measures
NRS	Pruritus Numerical Rating Scale
NOAEL	No observed adverse effect level
OX40	OX40 receptor (CD134)
OX40L	OX40 ligand (CD252)
PDE4	Phosphodiesterase type 4
PG	pharmacogenetic
PI	Principal Investigator

Abbreviation or Specialist Term	Explanation
PK	Pharmacokinetics(s)
PKAS	Pharmacokinetic analysis set
POEM	Patient-Oriented Eczema Measure
q2w	Every two weeks
q4w	Every four weeks
QTc	Corrected QT
SAE	Serious adverse event
SAS	Safety analysis set
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SC	Subcutaneous(ly)
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
SNOT-22	Sino-nasal Outcome Test
SoA	Schedule of Assessments
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time at which Cmax is observed
ULN	Upper limit of normal
USA	United States of America
vfPBMC	viably frozen peripheral blood mononuclear cells
WOCBP	Women of childbearing potential

5. INTRODUCTION

5.1. Background Information

[redacted]

5.2. Description of Study Drug

[redacted]

[redacted]

5.3. Nonclinical Experience

[redacted]

[redacted]

5.4. Clinical Experience

[redacted]

[redacted]

5.5. Benefit-Risk Assessment

[redacted]

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objectives

- To characterize the efficacy of ISB 830 monotherapy in adults with moderate-to-severe atopic dermatitis (AD) compared to placebo as measured by percentage change from baseline in EASI score at Week 16.

6.2. Secondary Objectives

- To evaluate safety, tolerability, PK and immunogenicity of ISB 830 in adults with moderate-to-severe AD.
- To measure the effect of ISB 830 on disease activity in adult subjects with moderate-to-severe AD, as measured by validated tools (such as IGA, EASI response, SCORAD).

6.3. Exploratory Objective

To evaluate pharmacodynamics (PD) of ISB 830 in adults with moderate-to-severe AD.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, double-blind, placebo-controlled study. The study will be conducted in 4 phases: a screening phase, a blinded treatment phase, an open-label treatment phase, and a follow-up phase. Subjects will participate in a 54-week treatment period (including 52 weeks of

study drug administration) with 12 weeks follow-up from the EOT visit (Week 54 to Week 66). The study will be conducted in 2 Parts, with dosing Groups 1-4 comprising Part 1, and dosing Groups 5-6 comprising Part 2.

The blinded treatment phase consists of a randomized, placebo controlled treatment with ISB 830 for 16 weeks at different dose levels (see below). The open-label treatment phase consists of a 38-week treatment phase where ISB 830 will be administered every other week (q2w) subcutaneously (SC). The primary endpoint of the study is assessed at the end of the blinded treatment period at Week 16.

Subject eligibility will be assessed during screening, which will occur within 28 days prior to randomization. During the screening period, treatments for AD will be withdrawn or modified for the subject as defined in Table 5. Subjects may be re-screened once (within or outside of the screening period) if they fail the screening evaluation. All screening procedures will be repeated during rescreening.

Subjects who continue to meet eligibility criteria will undergo Day 1/baseline (predose) assessments and will be randomized to equal groups of approximately 78 subjects each.

Subjects will receive subcutaneous (SC) injections of ISB 830, or corresponding placebo. A total of 27 doses (ISB 830 or placebo) will be administered q2w.

During the blinded treatment phase each subject will receive a dose on Day 1 and q2w starting from Day 15 through Week 14, according to the following treatment assignment below:

Study Part 1:

- Group 1: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume), starting at Day 15 (Week 2).
- Group 2: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by dosing every 4 weeks (q4w) of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted]) will be administered q4w starting at Day 15 (Week 2).
- Group 3: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q4w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted]) will be administered q4w starting at Day 15 (Week 2).
- Group 4: Dose of placebo (2 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (1 SC injection of [redacted]) starting at Day 15 (Week 2).

Study Part 2:

- Group 5: Dose of [redacted] ISB 830 (4 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (2 SC injections containing [redacted] volume), starting at Day 15 (Week 2).

- Group 6: Dose of placebo (4 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (2 SC injections of [redacted] starting at Day 15 (Week 2).

During the blinded treatment phase all subjects in Groups 1 through 4 will receive a loading dose consisting of 2 SC injections, followed by 7 maintenance doses consisting of 1 SC injection per dose. For Groups 5 and 6, all subjects will receive a loading dose consisting of 4 SC injections, followed by 7 maintenance doses consisting of 2 SC injection per dose, as described above and in Section 10.1, Table 6.

During the open-label treatment phase each subject will receive a dose of ISB 830 SC injection [redacted]) q2w (consisting of 1 to 2 SC injection per dose, respectively) from Week 16 to Week 52 or until subject withdrawal, as described above and in Section 10.1, Table 6.

All subjects in Groups 1-4 in the open-label treatment phase will receive [redacted] q2w. All subjects in Groups 5-6 in the open-label treatment phase will receive [redacted] q2w.

Safety assessments, clinical laboratory assessments, vital sign assessments, PK sampling, immunogenicity sampling, and clinical efficacy assessments (IGA and EASI) will be performed by the blinded Investigator and blinded study staff as defined in Table 2 of the protocol (Schedule of Assessments), or until the subject discontinues from the study. Study assessments will be performed at baseline (Day 1) and every week until Week 16. An experimental population PK design will be used for the PK blood sampling. The subjects in the rich PK group will have additional blood sampling between Days 1 to 8 (Week 1), and Days 85 to 92 (Week 12), compared to the sparse PK group. The subjects in the sparse PK group will have widespread sampling with fewer time points for each subject, compared to the rich PK subjects. Approximately 80 rich PK subjects will be randomized (in a 1:1:1:1 ratio) for Groups 1-4, and approximately 40 rich PK subjects will be randomized (in a 1:1 ratio) to Groups 5 and 6. The remaining subjects in the study will be included in the sparse PK group. Blood samples will be collected from the rich and sparse PK subjects according to the respective schedule described in Table 8 of the protocol.

End-of-treatment visits will be conducted on Day 113 (Week 16) for the blinded treatment phase and at Day 379 (Week 54) for the open-label treatment phase for all subjects. After the EOT visit, subjects should continue into the follow-up period and will have a follow-up phone call 4 weeks and 8 weeks after the EOT visit and a final clinic visit 12 weeks after the EOT visit.

Subjects who withdraw consent from the blinded treatment phase prior to Week 16 and are not continuing with treatment and/or entering the open-label treatment phase of the study will undergo the blinded treatment phase EOT visit procedures and enter the follow-up period for the GBR 830-204 study.

Subjects who withdraw consent from open-label treatment phase prior to Week 52 will undergo the open-label treatment phase EOT visit procedures and enter the follow-up period for the GBR 830-204 study.

All subjects continuing in the follow-up period will have a follow-up phone call 4 and 8 weeks after the EOT visit and a final clinic visit 12 weeks after the EOT visit as described in the Table 3 follow-up period.

Subjects will be clinically monitored for safety throughout the study, including anaphylactic reactions and/or injection site reactions (ISRs), with monitoring at the study site for 2 hours after

the first dose on Day 1 (in the blinded treatment phase) and on Day 113 (Week 16) (first dose in open-label treatment phase) and for 1 hour after dosing at all other visits.

Subjects who receive concomitant therapy with a prohibited medication during the study may have ISB 830 administration temporarily stopped for the duration of the prohibited treatment, including a washout period after last dose of prohibited medication of 4 weeks or 5 half-lives, whichever is longer. Administration of ISB 830 may then be resumed after the appropriate washout period and following discussion and upon obtaining written approval from the Sponsor's medical monitor.

To allow subjects access to the open-label treatment phase of the study, subjects who have completed the GBR 830-204 study prior to implementation of the amendment that includes the open label phase (eg, Protocol Amendment 3 (version 4.0) and/or Amendment 6 (version 7.0)) or who are in the follow-up phase of the study at the time of implementation of the open-label protocol amendment, may be eligible to participate in the open-label treatment phase of this study. Subjects who have completed the study prior to implementation of the open-label amendment must undergo a modified Screening visit (as per Table 2).

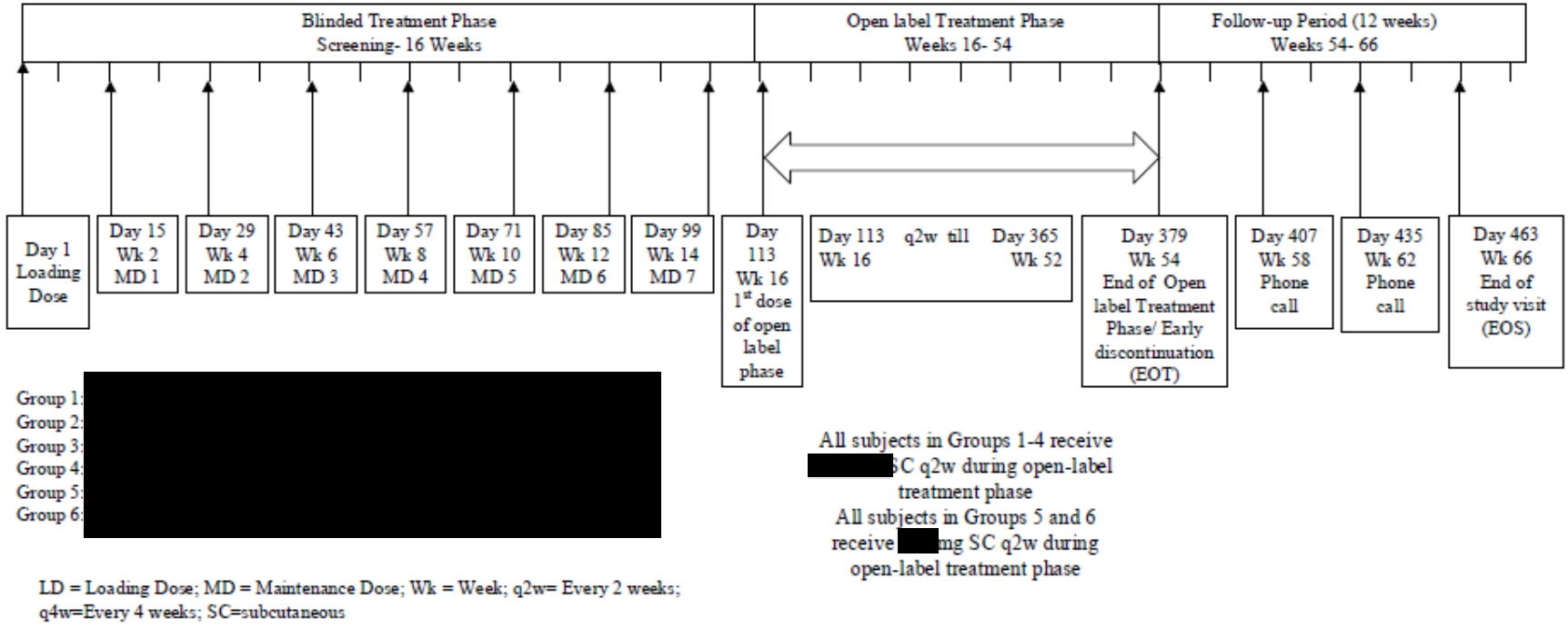
If eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1 and 5), subjects will undergo study assessments as per Table 3.

Subjects who are in the follow-up period of GBR 830-204 at the time the open-label protocol amendment is implemented must complete their follow-up period and then must undergo a modified Screening visit (as per Table 2). This includes a complete washout of any concomitant medications and therapies received (as per Table 5) prior to starting the open-label treatment phase of the study.

This includes a complete washout of any concomitant medications and therapies received (as per Table 5) prior to starting the open-label treatment phase of the study.

See Figure 1 for a schematic diagram of the study design and Table 2 and Table 3 for the Schedule of Assessments. The endpoints to be measured in this study are described in Section 15.3.

Figure 1: Study Design



LD = Loading Dose; MD = Maintenance Dose; Wk = Week; q2w= Every 2 weeks; q4w=Every 4 weeks; SC=subcutaneous

Table 2: Schedule of Assessments – Blinded Treatment Phase

Visit	SCR	Treatment Period (Day 1 – Week 16)																
Day	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15±1**	**29±1**	**43±1**	**57±1**	**71±1**	**85**	**86**	**89**	**90**	**92**	**99±1**	**113 ±1[1] End of Blinded Treatment Phase/Early Discontinuation (EOT)**
End of Week		**0**				**1**	**2**	**4**	**6**	**8**	**10**	**12**					**14**	**16**
Written informed consent[2]	x																	
Inclusion and exclusion criteria	x	x																
Medical and surgical history[3]	x																	
Demographics	x																	
Prior and concomitant medications[4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height and weight[22]	x																	
Vital signs	x	x				x	x	x	x	x	x	x	x				x	x
Physical examination[5]	x	x				x	x	x	x	x	x	x	x				x	x
12-Lead ECG[6]	x	x																x
TB testing	x																	
Clinical Laboratory	x	x					x	x		x		x						x
Pregnancy test[8]	x	x						x		x		x						x
Serology testing[9]	x																	
Immunogenicity blood samples[10]		x					x			x		x					x	x
Blood samples for biomarkers (serum and/or plasma)[11]	x	x				x	x	x		x		x					x	x

Table 2: Schedule of Assessments – Blinded Treatment Phase (Continued)

Visit	SCR	Treatment Period (Day 1 – Week 16)															
Day	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15±1**	**29±1**	**43±1**	**57±1**	**71±1**	**85**	**86**	**89**	**90**	**92**	**99±1**	**113 ±1[1] End of Blinded Treatment Phase/Early Discontinuation (EOT)**
End of Week		**0**				**1**	**2**	**4**	**6**	**8**	**10**	**12**					**14**	**16**
Blood samples for vfPBMC and/or cell subsets	x	x				x	x	x		x		x					x	x
Optional PG (pharmacogenetic) testing and collection of the whole blood (DNA) sample	x[7]																	
Rich PK group blood samples[13]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Sparse PK group blood samples[14]							x	x	x	x	x	x					x	x
Required AD photography[12]		x				x	x	x		x		x					x	x
Dispense electronic subject diary [15]	x																	
Pruritus NRS[16]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
POEM, DLQI, EQ-5D, HADS[17] (Subject completed)	x	x				x	x	x	x	x		x						x
IGA, EASI, GISS, SCORAD, BSA (Investigator completed)	x	x				x	x	x	x	x		x						x

Table 2: Schedule of Assessments – Blinded Treatment Phase (Continued)

Visit	SCR	Treatment Period (Day 1 – Week 16)															
Day	**-28 to -1**	**1**	**2**	**5**	**6**	**8**	**15±1**	**29±1**	**43±1**	**57±1**	**71±1**	**85**	**86**	**89**	**90**	**92**	**99±1**	**113 ±1[1] End of Blinded Treatment Phase/Early Discontinuation (EOT)**
End of Week		**0**				**1**	**2**	**4**	**6**	**8**	**10**	**12**					**14**	**16**
ACQ-5 [18], SNOT-22 [19] (Subject completed)	x	x																x
Patient Global Assessment of Disease	x	x					x	x	x	x		x						x
Patient Global Assessment of Treatment							x	x	x	x		x						x
Assess sick-leave and/or missed school days[16]	x	x						x		x		x						x
Randomization[20]		x																
Study drug administration[1, 21]		x					x	x	x	x	x	x					x	x[OLE]
Adverse events assessment	x ----------x																	

ACQ-5 = Asthma Control Questionnaire; AD = atopic dermatitis; BSA = body surface area; DQLI = Dermatology Quality of Life Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EOT = End of Treatment Visit; EQ-5D = EuroQol-5D; FSH = follicle stimulating hormone; FU = follow-up; GISS = Global Individual Signs Score; h = hour; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; NRS = Numerical Rating Scale; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing of Atopic Dermatitis; SCR = Screening; SNOT-22 = Sino-nasal Outcome Test; TB = tuberculosis; Wk = Week. **Note:** Visits do not include a Day 0. If at any time point, the different assessments coincide, the following sequence will be used: vital signs – ECG – blood sample(s) – AD photography – dosing. The last follow-up visit will be considered the end-of-study visit.

Footnotes begin on next page.

Footnotes:

1. The subset of subjects who have completed the GBR 830-204 study prior to implementation of the amendment that includes the open-label phase (eg, Protocol Amendment 3 [version 4.0] and/or Amendment 6 [version 7.0]), and provide informed consent to participate in the open-label treatment phase of the study, must undergo the modified Screening Visit. Subjects who are in the follow-up period of GBR 830-204 at the time the open-label protocol amendment is implemented, must complete their follow-up period as per Protocol, and then must undergo a modified Screening visit per Section 14.2.2.
   All blinded treatment phase assessments must be completed including PK and immunogenicity sampling prior to any open-label treatment phase assessments and dosing. In the event of early withdrawal from the blinded treatment phase, the EOT Week 16 (Day113,) procedures will be performed as soon as possible after a subject withdraws from the study. **The first open-label dose will be administered on Week 16 (Day 113).** Subjects will be clinically monitored by study site personnel for 2 hours following the Week 16 dose.
2. Written informed consent for the study; informed consent for optional Rich PK, and optional pharmacogenetic (DNA) testing.
3. Medical history includes recent medical history (any illness occurring within past 4 weeks), previous medical history (only significant medical or surgical illness), smoking, alcohol and intake of drugs of abuse). In addition, medical history will include history of allergy to *Dermatophagoides species* (house dust mite), birch oak, cockroach, cat dander, dog dander, Bermuda grass.
4. On Days 2, 5, 6, 87-92, these procedures will be performed for subjects in the rich PK analysis set only. Subjects in the sparse PK analysis set will not have a study visit on Days 2-6 and 87-106.
5. A physical exam is required at all visits. At screening a comprehensive physical exam is required. At all other visits, a symptom directed/targeted physical exam is required. Comprehensive physical exam includes general appearance, skin/subcutaneous tissue, head and neck (including thyroid gland), eyes, ears, nose and throat, mouth, abdomen, lymph nodes, musculoskeletal, thorax, lungs/respiratory, heart/cardiovascular, urogenital, anal/rectal, extremities and a brief neurological/psychiatric examination. Urogenital and anal/rectal examinations are optional.
6. On Day 1, ECG will be performed predose and at 30 minutes (±30 minutes) postdose.
7. Optional PG sample can be collected at any time during the study.
8. For women of childbearing potential: A urine pregnancy test may be performed at the initial screening visit, at the Investigator's discretion. A serum pregnancy test is required within 7 days prior to randomization and at the final end of study follow-up visit Week 66 (Day 463); all other visits may have urine pregnancy tests that must be performed predose. The pregnancy test performed predose on Day 1 may be a urine test and must be negative prior to randomization. Postmenopausal women: Must have FSH testing at screening.
9. Virus serology will be performed by a central laboratory. See Appendix 1 in the protocol for a list of tests.
10. Samples will be collected from all subjects for immunogenicity analysis at pre-dose (within 15 minutes before drug administration) on Day 1, Day 15, Day 57, Day 85, and Day 99; and at the blinded treatment phase EOT (Day113) and at the final 12-week Follow-up visit.
11. Samples will be collected for biomarker analysis pre-dose (within 15 minutes before drug administration) on Day 1, Day 8, Day 15, Day 29, Day 57, and Day 85; and at the blinded treatment phase EOT (Day 113).
12. Photographs will be taken of representative areas of AD-involved skin, for example, the same lesional area(s) used for SCORAD assessments (with the exception of the subject's face, which should not be photographed to maintain subject's anonymity). Refer to the photography manual for additional details.
13. Serum samples for the rich PK group only (n=20/arm) will be obtained on: Dose 1 (Day 1): Predose (within 15 minutes prior to 1st dose), and post dose at 4 h, 24 h (Day 2), 96 h (Day 5), 120 h (Day 6), 168 h (Day 8), and 336 h (Day 15), predose, (within 15 minutes prior to 2nd dose); Dose 3, 4, 5, 6, and 8 (Day 29, Day 43, Day 57, Day 71, and Day 99): Predose (within 15 minutes prior to dose); Dose 7 (Day 85): Predose (within 15 minutes prior to dose) and post dose at 4 h, 24 h (Day 86), 96 h (Day 89), 120 h (Day 90), 168 h (Day 92), and Day 113 (Week 16): pre-dose (within 15 minutes of first open-label dose, and final follow-up visit Week 66 (Day 463). See Table 8 for windows.
14. Serum samples for the sparse PK group will be collected from all subjects (n=58/arm): Dose 2, 3, 4, 5, 6, 7, 8 (Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and Day 99): Predose (within 15 minutes prior to dose); Day 113 (Week 16): pre-dose (within 15 minutes of first open-label dose and final follow-up visit Week 66 (Day 463). See Table 8 for windows.
15. Minimum of 3 days of diary in the week prior to randomization.
16. Pruritus NRS and sick leave and/or missed school days assessments will be completed by the subject.
17. Administered to a sub-set of subjects who fluently speak the language in which these questionnaires are translated.
18. ACQ-5: Only to a subset of subject with a medical history of asthma.
19. SNOT-22: Only to a subset of subjects eg, with chronic rhinitis/rhinosinusitis nasal polyps, allergic rhinitis.
20. Day of randomization and first dosing are assumed to be the same, no waiver allowed.

21. Study drug administration: Subcutaneous
22. Height will be assessed at screening only.

Table 3: Schedule of Assessments – Open-label Treatment Phase

Period	**Treatment Period**							**End of Open-label Treatment Phase/Early Discontinuation**[1]	**Follow-up**[8]	
End of Week	**18**	**20**	**22**	**24**	**26**	**28**	**Long-term Assessments (Week 26 onwards)**[7]	**54**	**58, 62 Safety phone call**[9]	**66 (EOS) In Clinic**
Visit								**EOT**		
Day	**127 ±2**	**141 ±2**	**155 ±2**	**169 ±2**	**183 ±2**	**197 ±2**	**211 ±2 to 365 ±2**	**379**	**407 ± 5 435 ± 5**	**463 ± 5**
Prior and concomitant medications	X	X	X	X	X	X	Every **2** Weeks (Last visit +14 days)	X	X	X
Vital signs	X	X	X	X	X	X	Every **2** Weeks (Last visit +14 days)	X		X
Physical examination[2]	X	X	X	X	X	X	Every **2** Weeks (Last visit +14 days)	X		X
Weight										X
12-Lead ECG								X		X
Clinical Laboratory[3]	X				X		Every **8** Weeks (Last visit +56 days)	X		X
Pregnancy test[4]		X		X		X	Every **4** Weeks (Last visit +28 days)	X		X
Immunogenicity blood samples[5]	X	X				X		X		X
PK blood samples[5]	X	X				X		X		X
IGA, EASI (Investigator completed)	X		X		X		Every **4** Weeks (Last visit +28 days)	X		X
AD photography		X		X		X	Every **4** Weeks (Last visit +28 days)	X		X
Blood samples for biomarkers (serum and/or plasma)		X		X		X				
Blood for vfPBMC and/or cell subsets		X		X		X				
Study drug administration[6]	X	X	X	X	X	X	Every **2** Weeks (Last visit +14 days)			
Adverse events assessment	X----------X									

EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FSH = follicle stimulating hormone; HEENT = head, eyes, ears, nose and throat; IGA = Investigator's Global Assessment; PK = pharmacokinetics; SoA = schedule of assessment.

Note: If at any time point, the different assessments coincide, the following sequence will be used: vital signs – ECG – blood sample(s). The last follow-up visit will be considered the end-of-study visit.

1. In the event of early withdrawal, during the open-label treatment period, EOT procedures as described at Week 54, (Day 379) will be performed as soon as possible after a subject withdraws from the study (unless the subject withdraws consent).
2. A physical exam is required at all visits. At screening a comprehensive physical exam is required. At all other visits, a symptom directed/targeted physical exam is required. A comprehensive physical examination will include head, eyes, ears, nose and throat (HEENT), cardiovascular system, respiratory system, musculoskeletal system, skin (non-atopic dermatitis related), gastrointestinal system, genitourinary system, and a brief neurological examination. Sign/symptom-directed examination might be performed as per the investigator's discretion.
3. Clinical laboratory assessments (hematology, biochemistry, and urinalysis) will be performed by a central laboratory.
4. A urine pregnancy test will be performed predose. A serum pregnancy test is required at the 12 week final EOS Visit, Day 463 (Week 66).
5. Blood samples for immunogenicity and PK analysis should be collected within 15 minutes prior to study drug administration when occurring on dosing days, at EOT, and at Follow-up. The actual time of sample collection and study drug administration for all visits with PK evaluations will be recorded.
6. Study drug administration: Subcutaneous administration (see Section 10.5 of the protocol) will be administered q2w. Subjects will be clinically monitored by study site personnel for 1 hour after all doses (Week 18 onwards). The actual time of sample collection and study drug administration for all visits with PK evaluations will be recorded.
7. Long-term assessments: Every 2 weeks concomitant medication, vital signs, and physical examinations per the SoA table.
   Long-term assessments: Every 4 weeks AD photography, IGA, EASI, and urine pregnancy tests per the SoA table.
   Long-term assessments: Every 8 weeks Clinical Laboratory safety assessments per the SoA table.
8. For a subject who prematurely discontinues blinded or open-label treatment, the follow-up period will consist of a phone call 4 weeks and 8 weeks after the appropriate EOT visit and a final follow up visit 12 weeks after the appropriate EOT visit.
9. Safety phone call to include collection of AEs and concomitant medications.

7.1.1. Study Rationale

[redacted]

7.1.2. Dosing Rationale

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.3. Estimated Duration of Subject Participation

The anticipated maximum total study duration for each subject is approximately 70 weeks. This duration will consist of the screening period of up to 4 weeks, the blinded treatment period of up to 16 weeks (14 weeks of treatment, with a loading dose on Day 1 followed by maintenance dosing from Day 15 [Week 2] until the last dose at Week 14), the open-label treatment period of up to 38 weeks, and the follow-up period of 12 weeks starting at the end of the open-label treatment period. Subjects who consent to participate in the open-label treatment phase of the study after they completed the GBR 830-204 study, and require a modified screening visit would have a study participation duration of up to 86 weeks.

7.1.4. Number of Subjects (Planned)

For Groups 1 through 4, a sufficient number of subjects will be screened to randomize 312 eligible subjects in a 1:1:1:1 ratio. For Group 5 and 6, a sufficient number of subjects will be

screened to randomize 156 eligible subjects in a 1:1 ratio to either ISB 830 or Placebo, therefore approximately 468 subjects are planned to be randomized in this study. The randomization will be stratified by disease severity (moderate or severe, as assessed by IGA), geographic region (North America vs European Union), and subjects consenting to rich PK sampling (Yes/No). The actual number of subjects randomized in Groups 5 and 6 may be different than initially planned due to the impact of the SARS-CoV-2/COVID-19 pandemic (see Section 8.3.4).

7.2. Treatment Assignment

Study participation begins (ie, the subject is enrolled in the study) once written informed consent is obtained (see Section 18.3 for details). Once informed consent is obtained at Screening, the subject will be assigned a subject screening number using the interactive voice response system/interactive web response system (IVRS/IWRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The subject screening number will be used to identify the subject during the screening process.

A subject who fails screening (ie, does not meet eligibility criteria) will be given a new screening number if he/she is re-screened for the study. The subject's original screening number will not be re-assigned to another subject.

Subjects who meet all eligibility criteria will be randomized on Day 1 using the IVRS/IWRS system and allocated a randomization number prior to receiving the first dose of study drug. Randomized subjects will be stratified by the IVRS/IWRS based on disease severity, geographic region, and subjects consenting to rich PK sampling (Yes/No) to ensure balance of treatment groups within each stratum.

For the open-label treatment phase, the first dose will be administered 2 weeks after the last dose in the blinded treatment phase to maintain the dosing regimen. Subjects in Groups 1-4 will receive [redacted] and subjects in Groups 5-6 will receive [redacted] SC doses of ISB 830 q2w until study completion, discontinuation or withdrawal.

Randomized subjects who terminate their study participation for any reason, regardless of whether study drug has been taken or not, will retain their randomization number.

To allow subjects access to the open-label treatment phase of the study, subjects who have completed the GBR 830-204 study prior to implementation of the open-label protocol amendment or who are in the follow-up phase of the study at the time of implementation of the open-label protocol amendment, may be eligible to participate in the open-label treatment phase of this study. These subjects will be assigned a new screening number.

Subjects who have completed the study prior to implementation of the open-label protocol amendment must undergo a modified Screening visit (as per Table 2), and if eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1 and 5), will undergo study assessments as per Table 3. This includes a complete washout of any concomitant medications and therapies received (as per Table 5) prior to starting the open-label treatment phase of the study.

Subjects who are in the follow-up period of GBR 830-204 at the time the open-label protocol amendment is implemented, must complete their follow-up period and then must undergo a modified Screening visit (as per Table 2), and if eligibility criteria are met (with the exception of

inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1and 5), will undergo study assessments as per Table 3. This includes a complete washout of any concomitant medications and therapies received (as per Table 5) prior to starting the open-label treatment phase of the study.

7.3. Dose Adjustment Criteria

No dose modifications for a subject are allowed in the blinded treatment phase.

See Section 8.3.1 for criteria regarding temporary discontinuation of study drug.

7.4. Criteria for Study Termination

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/Institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The Institutional Review Board (IRB)/independent Ethics Committee (IEC) will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/Institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue his/her participation in the study should his/her judgment so dictate. If the Investigator terminates or suspends his/her participation in the study without prior agreement of the Sponsor, the Investigator should inform the Institution where applicable, and the Investigator/Institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

7.5. End of the Study

The end of the study (study completion) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. Materials or supplies provided by the Sponsor may be returned to the Sponsor or designee upon study completion, as directed by the site monitor. The Investigator will notify the IRB/IEC when the study has been completed.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Provide written informed consent and any locally required authorization prior to any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with all aspects of the protocol.
3. Male or female ≥18 years at the time of screening.
4. Physician diagnosis of AD for > 1 year; diagnosis of AD as defined by the American Academy of Dermatology Consensus Criteria (Eichenfeld et al, 2014).
5. AD involvement of ≥10% body surface area (BSA) at screening and baseline.

6. EASI score of ≥12 at screening or ≥16 at baseline.
7. IGA score of ≥3 at screening and baseline (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe).
8. Baseline Pruritus Numerical Rating Scale (NRS) score for maximum itch intensity ≥3 over the previous 24 hours. A minimum of 3 days of diary completion is required in the week prior to randomization.
9. Documented/reported recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications (topical corticosteroids or crisaborole or topical calcineurin inhibitors) or subjects for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks as defined in the protocol). Documents may include medical records, physician to healthcare provider communication (with date and time of communication and physician signature) or pharmacy records (with clearly listed dates of dispensation). A course of marketed systemic immunosuppressants (eg, prednisone, cyclosporine, methotrexate) for AD in the 6 months prior to screening assumes failure of topicals and is acceptable in place of topical failure.
10. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (with the exception of prohibited moisturizers containing additives listed in Exclusion Criteria #5).
11. Must agree to the following requirements during the study:
    a. If female and of childbearing potential, she must have a negative serum pregnancy test result within 7 days prior to first dosing and a negative urine pregnancy test predose on Day 1. She must be willing to use a highly effective form of contraception (ICH E8 Guideline, 1997; ICH M3[R2] Guidance, 2009; FDA M3[R2] Guidance, 2010) for the duration of the study and for at least 3 months after the last dose of study medication. Methods like periodic abstinence, post ovulation procedures and withdrawal are not considered adequate. Each woman will be considered to have childbearing potential unless she has been surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy or has been post-menopausal for at least 2 years. For postmenopausal women only, follicle stimulating hormone (FSH) testing will be performed at screening to confirm non-childbearing potential (FSH ≥40 IU/L).
    b. If male with a partner of childbearing potential, he must be willing to use condoms in combination with a second effective method of contraception during the study. Each man will be considered as potent unless surgically sterilized (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate). Male subjects must continue to use contraception for 180 days following administration of the study drug.
    c. Male subjects should agree not to donate sperm during the study and for 180 days following administration of the study drug.

8.2. Subject Exclusion Criteria

1. Prior treatment with ISB 830.

2. Employee of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
3. Concurrent enrollment in another investigational clinical study.
4. Treatment with any of the following before baseline:
    a. Investigational biological agent within 8 weeks of baseline or 5 half-lives, whichever is longer.
    b. Investigational drugs, eg, phosphodiesterase type 4 (PDE4) inhibitors, Janus kinase (JAK) inhibitors, within 4 weeks of baseline.
    c. Phototherapy for AD within 4 weeks of baseline.
    d. Marketed drugs, including systemic corticosteroids, immunosuppressive/immunomodulatory drugs including but not limited to cyclosporine, mycophenolate mofetil, interferon-gamma (IFN-γ), PDE4 inhibitors, JAK inhibitors, azathioprine or methotrexate, within 4 weeks of baseline.
    e. Topical medications, including corticosteroids, tacrolimus, and/or pimecrolimus and crisaborole within 1 week of baseline.
    f. Regular use (>2 visits/week) of a tanning booth/parlor within 4 weeks of baseline.
    g. Biologics, depending on the type of biologic such as cell-depleting agents including but not limited to rituximab: within 6 months of baseline, or until lymphocyte and CD19+ lymphocyte count returns to normal, whichever is longer.
    h. Biologics including infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, etanercept, anakinra, dupilumab: within 12 weeks of baseline, or 5 half-lives, whichever is longer.
    i. Other biologics: within 5 half-lives (if known).
5. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (subjects may continue using stable doses of such moisturizers if initiated before the screening visit).
6. Planned or anticipated use of any prohibited medications and procedures during study treatment as defined in the study protocol.
7. Subjects who are immunocompromised (congenital or acquired), or who have had a recent (within 3 months prior to baseline) or current serious systemic infection (including infectious mononucleosis-like illness or herpes zoster).
8. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit.
9. Subjects who have evidence of active or latent tuberculosis (TB) as documented in their medical history, or test positive at screening. For indeterminate cases an informed decision will be made between the Principal Investigator and Medical Monitor.
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: subjects may be rescreened after infection resolves.
11. Presence of skin comorbidities that may interfere with study assessments, in the opinion of the Investigator, including subjects with psoriasis.

12. Poorly controlled asthma as assessed by the Asthma Control Questionnaire [ACQ-5] based on International ERS/ATS guidelines.
13. Any condition at baseline which is part of the criteria for discontinuation of study drug as defined in the study protocol.
14. Subjects who are known to be seropositive for human immunodeficiency virus (HIV) or who test positive at screening.
15. History of a positive result for Hepatitis B surface antigen (HBsAg), antibody to Hepatitis B core antigen (anti-HBcAg), or antibody to Hepatitis C virus (anti-HCV) or presence of these findings at screening.
16. History of alcohol or drug abuse within 2 years of the screening visit.
17. Subjects with a history of non-malignant lymphoproliferative disorders, or a history of malignancy within 5 years before baseline (except completely treated in situ cervical carcinoma or non-metastatic squamous or basal cell carcinoma of the skin).
18. In the opinion of the Investigator, subjects with any other medical or psychological condition as well as laboratory values, which are significantly different from normal reference ranges and/or judged to be clinically significant; and/or any condition that would interfere with evaluation of the study drug or interpretation of subject safety or study results, including conditions that are inadequately understood at the time of screening.
19. Subjects with a history of substance abuse or dependence that in the opinion of the Investigator, is considered to interfere with the subject's participation in the study.
20. Planned or anticipated major surgical procedure during the subject's participation in this study.
21. Women who are pregnant or breast feeding.
22. Known hypersensitivity to monoclonal antibodies or any of the excipients of the study drug.

8.3. Subject Withdrawal Criteria

A subject may voluntarily discontinue study participation at any time after giving informed consent and before the completion of the last visit of the study. Subjects may also be withdrawn from study drug treatment at the discretion of the Investigator or Sponsor for safety, noncompliance, or administrative reasons.

The reasons for subject withdrawal will be recorded and may include, but are not limited to:

1. Withdrawal of consent by the subject to continue in the study. If consent is withdrawn, the subject will not receive any further investigational product (IP) or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.
2. Development of a serious or intolerable adverse event (AE) that necessitates discontinuation at the discretion of the Investigator including but not limited to:

- Anaphylactic reaction or other severe systemic reaction to study drug injection (see Section 13.2.1.4).
- Diagnosis of a malignancy (new or relapse) during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status.
- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks.

3. Severe laboratory abnormalities:
   - Serum creatinine > 1.5 mg/dL (equivalent to Système International (SI) unit of >114.39 µmol/L).
   - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) values >3x upper limit of normal (ULN) with total bilirubin >2x ULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome).
   - Absolute neutrophil count ≤ 500/µL (equivalent to SI unit of ≤ $0.5x10^9$/L) or absolute lymphocyte count ≤600/µL (equivalent to SI unit of ≤$0.6x10^9$/L) or platelet count ≤50,000/µL (equivalent to SI unit of ≤$50x10^9$/L) or any abnormal evaluations which in the opinion of the Investigator are clinically significant.

     Confirmed AST and/or ALT >5x ULN (for more than 2 weeks).
4. At the discretion of the Investigator, when he/she believes continued participation is not in the best interest of the subject.
5. At the discretion of the Investigator, when the subject does not adhere to the study procedures.
6. A positive pregnancy test.
7. A female partner of a male study subject becomes pregnant.
8. A protocol deviation that, in the opinion of the Sponsor and Investigator, warrants discontinuation from the study.

A subject who is withdrawn from blinded or open-label study drug treatment will be asked to complete all procedures scheduled for the EOT visits at time of withdrawal (Week 16, or Week 54, respectively). The subject should continue to the follow-up period for a phone call 4 weeks and 8 weeks after the EOT visit and a final follow up visit 12 weeks after the EOT visit, unless the subject withdraws consent or is lost to follow-up.

8.3.1. Temporary Discontinuation of Study Drug

1. Rescue treatment for AD (drug or phototherapy or both) given based on the opinion of the Investigator; subjects who require rescue therapy will be considered as treatment failures. Subjects who receive topical medication as rescue treatment will continue study drug treatment. Subjects who receive rescue treatment with systemic corticosteroids or

non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) or biologics (eg, dupilumab) will be immediately discontinued from study drug treatment but will continue with all other study assessments as per Table 2 . Administration of ISB 830 may be resumed after the appropriate washout period, (as per Table 5) following discussion, and upon obtaining written approval from the Sponsor's medical monitor.

2. Subjects must be temporarily discontinued from study drug dosing in the event of:
   - Grade 3 neutrophil count (<1000-500/μL, per the National Institutes of Health/National Cancer Institute (NIH/NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (CTCAE v4.03, 2010).
   - Grade 2 platelet count (<7.5 – 5.0 X 10^4/μL, per NIH/NCI-CTCAE).
   - Fever (>100.4°F or >38°C), suspected infection, or infection requiring oral antibiotics.

If temporarily discontinued from study drug dosing, a subject may resume dosing when the abnormal values are within normal reference ranges. The decision to discontinue dosing a subject due to an AE will be made on the basis of clinical severity and relatedness to the study drug. It is recommended that the Investigator consult with the Sponsor's medical monitor before removing the subject from the study.

8.3.2. Lost to Follow-up

A subject will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status. Subjects refusing to return to the site or to continue participation in the study when contacted, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol (ie, the subject should continue to the next scheduled visit relative to their Day 1 visit).

8.3.3. Permanent Discontinuation of Study Drug

A subject who is permanently discontinued from further receipt of study drug, regardless of the reason (withdrawal of consent, due to an AE, other reason), will be identified as having permanently discontinued treatment.

A subject who is permanently discontinued from receiving study drug during the blinded or open-label treatment phases will be asked to complete all procedures scheduled for the EOT visits (Week 16, or Week 54, respectively). A subject who is withdrawn from study drug treatment should continue to the follow-up period, unless the subject withdraws consent, is lost to follow-up, or is enrolled in another clinical study.

8.3.4. Enrollment of Additional Subjects

Special considerations have been added to the protocol based on the issues arising from the SARS-CoV-2/COVID-19 pandemic. During the blinded dosing period for Part 2 (ie, prior to

completion of the Week 16 visit), any randomized subject who terminates study participation or who misses 2 or more consecutive doses of study drug (even if continuing with study participation) or misses any part of the primary endpoint assessments at Week 16, as a result of pandemic-related reasons, may not be counted against the total number of subjects targeted (N=156 for Part 2 of the study). For each of these cases, a new subject may be screened and randomized, to allow an evaluable number of subjects for the Week 16 primary endpoint. The new subjects in screening will receive new subject numbers and new treatment assignments as per the current randomization schedule in the protocol.

Additional subjects will only be added in response to the number of subjects who meet the above criteria, as a result of pandemic-related issues. Randomized subjects who discontinue study participation or miss consecutive doses or the Week 16 primary endpoint assessments for non-pandemic related reasons, or who have study drug or study visit issues after completing their Week 16 visit, will not trigger the screening of additional subjects.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

The following study drugs will be supplied by Ichnos Sciences SA for the study:

Table 4: Study Drugs

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

9.2. Concomitant Medications and Therapy

9.2.1. Prior Medications

The following medications and therapies listed in Table 5 are excluded for the designated length of time prior to Baseline (Day 1) and prior to Week 16 (Day 113) for those subjects who completed the study and re-enter only the open-label treatment phase of the study.

Table 5: Excluded Concomitant Medications and Therapies

Medication	Duration of Washout, Prior to Baseline
Investigational biological agent	8 weeks or 5 half-lives, whichever is longer
Investigational drugs eg, phosphodiesterase type 4 (PDE4) inhibitors, Janus kinase inhibitors (JAK inhibitors)	4 weeks
Phototherapy for AD	4 weeks
Marketed drugs, including systemic corticosteroids, immunosuppressive/immunomodulatory drugs including but not limited to cyclosporine, mycophenolate mofetil, IFN-γ, PDE4 inhibitors, JAK inhibitors, azathioprine, methotrexate	4 weeks
Topical medications including crisaborole, corticosteroids, tacrolimus, and/or pimecrolimus	1 week
Regular use (>2 visits/week) of a tanning booth/parlor	4 weeks
Cell-depleting agents including but not limited to rituximab	6 months or until lymphocyte and CD19+ lymphocyte count returns to normal, whichever is longer
Infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, etanercept, anakinra, dupilumab	12 weeks or 5 half-lives, whichever is longer
Other biologics (not listed above)	5 half-lives (if known)
Live (attenuated) vaccine	12 weeks

AD = atopic dermatitis; IFN γ = interferon gamma; JAK = Janus kinase; PDE4 = phosphodiesterase 4.

9.2.2. Permitted Concomitant Medications and Therapies

All restrictions on the medications listed above in Table 5 are applicable for the entire duration of the study. Other concomitant medications that the subject receives on a regular basis may continue, if in the opinion of the Investigator, it does not put the subject at undue risk or does not interfere with the study evaluations.

All subjects who require rescue therapy are considered as treatment failures. Subjects who receive topical medication as rescue treatment will continue study treatment. Subjects who receive rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) or biologics (eg, dupilumab) will be immediately discontinued from study drug treatment and will continue with all other study assessments as per Table 2. Administration of ISB 830 may be resumed after the appropriate washout period (4 weeks or 5 half-lives, whichever is longer) and following discussion and upon obtaining written approval from the Sponsor's medical monitor.

9.2.3. Prohibited Concomitant Medications and Therapies

All the medications and therapies listed above in Table 5 are prohibited for the entire duration of the study beginning from the time indicated before the baseline visit (Day 1), unless they are required, in the opinion of the Investigator, for the treatment of an AE. If a subject receives

systemic steroids or other systemic immunosuppressive drugs for non-AD related conditions, treatment with study drug must be stopped immediately. After treatment with these medications is completed, treatment with study drug may be re-instituted after a washout period and deemed appropriate after discussion with the medical monitor and Sponsor, however study drug may not be re-instituted earlier than 5 times the half-life of the medication. Please refer to the study reference manual for more details regarding minimum washout periods.

9.2.4. Lifestyle and/or Dietary Restrictions

Subjects will be requested to adhere to the following restrictions:

- Subject must be willing to use a highly effective form of contraception, as described in Section 8.1.
- Abstain from regular use (>2 visits/week) of a tanning booth/parlor within 4 weeks prior to baseline and during the study, through Week 66.
- Topical steroids will be prohibited during the study through Week 66.
- Emollients may be used during the study. Subjects may continue use of these emollients during the study if using stable doses of such emollients, and if treatment was initiated before the screening visit. However, emollients containing additives listed in Exclusion criterion 5 (eg ceramide, hyaluronic acid, urea, or filaggrin degradation products) may not be initiated during the screening period or at any time during the study.

Antihistamines may be used during the study, including use in the follow-up period.

9.3. Treatment Compliance

Treatment compliance will be measured by the designated person (see Section 10.5) at the clinical study site.

Records of drug administration and drug accountability must be maintained to document compliance of treatment administration for each subject and will be reviewed by the unblinded clinical monitor.

9.4. Randomization and Blinding

See Section 7.2 regarding randomization and allocation to treatment groups.

9.4.1. Blinding and Unblinding Procedures

This is a double-blind study in which ISB 830 and placebo are not indistinguishable in appearance and viscosity. For the blinded treatment phase, neither the subject/legal representative nor any of the Investigator or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received. Since ISB 830 and placebo are not indistinguishable, the study drug will be handled/prepared by a designated unblinded study drug administrator (eg, unblinded pharmacist or designee) at the site and will be administered by a designated unblinded study team member who will not be involved in the management of study subjects. An unblinded clinical monitor (Clinical Research Associate [CRA]) will perform study drug accountability.

To enable the bioanalysis of ISB 830 in serum samples only from the active treatment groups, the randomization codes will be shared with a designated person at the bioanalytical site. It will be ensured that this will not unblind the subject, investigators or sponsor staff involved in the study.

For the blinded treatment phase, in the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, or needs to be known to treat an individual subject for an AE, the medical monitor must be notified immediately by the Investigator and if possible, before unblinding.

For the open-label treatment phase, drug preparation and administration should be handled by the same unblinded personnel as for the blinded treatment phase.

In special circumstances (eg, during SARS-CoV-2/COVID-19 pandemic, which may prevent the subject from presenting to the site), the handling, preparation, and administration of the study drug (during blinded or open-label periods of the study) may be performed by an unblinded, qualified healthcare provider who is not involved in study management, such as a home-visit nurse contracted by the Sponsor (if such service is available at the time and where permitted by local regulations) (see Section 10.5).

9.4.2. Unblinding in the Event of a Medical Emergency

In the event of a medical emergency during the blinded treatment phase, the Investigator may unblind an individual subject's study drug allocation. In such emergencies, the investigator may contact the Sponsor's medical monitor for drug specific input prior to disclosure of the treatment allocation. However, the Investigator will make the decision to unblind the treatment assignment.

Instructions for unblinding an individual subject's study drug allocation are contained in the IVRS/IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received IP. In the majority of cases, the management of a medical emergency would be the same whether or not IP was received by the subject. If this was the case, the study drug allocation should not be unblinded.

In the event of unblinding, the following minimum information will be recorded in a memo to file and signed by the Investigator. The information will be reported in the CSR.

- Date of unblinding.
- Identification of person(s) requesting the unblinding.
- Reason for unblinding.

If the breaking of the blind was due to an AE, the subject should be followed up until the AE has resolved or stabilized.

Unblinding is not applicable for the open-label treatment phase of the study.

9.5. Subject Completion

An individual subject will be considered to have completed the study if the subject completed the End of Study visit, with a minimum of 1 dose of study drug received.

Subjects who permanently discontinue from study drug in the blinded treatment or open-label treatment phase and who do not withdraw consent from the study will be asked to return to the clinic for an End of Treatment (EOT) assessment and should continue with follow-up study visits.

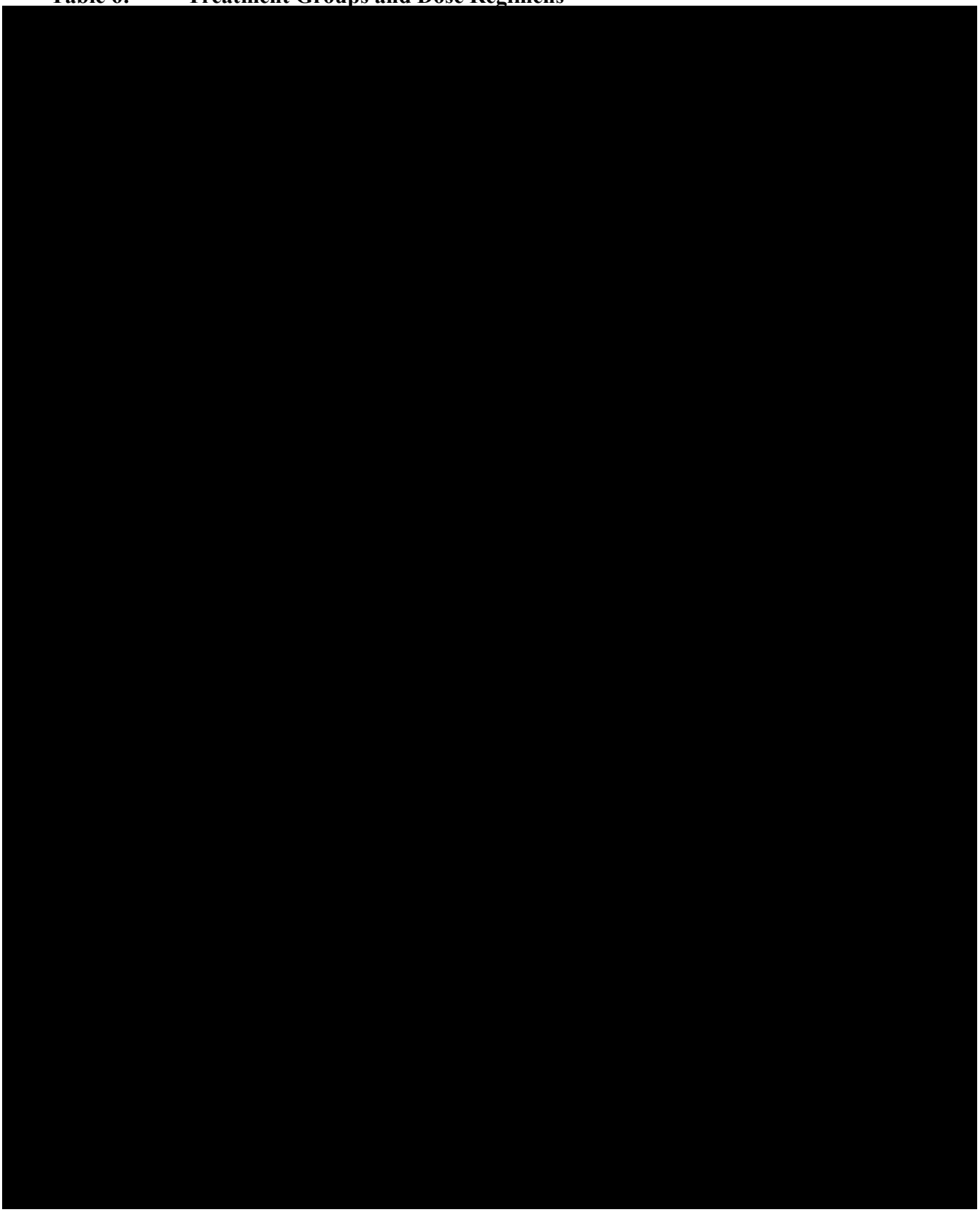
Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 8.3) and the End of Study visit was not completed.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

A description of treatment groups and their respective dose regimens is provided in Table 6. For the blinded treatment phase of the study, all subjects in treatment groups 1-4 will receive a loading dose consisting of 2 SC injections, and maintenance dosing consisting of 1 SC injection per dose, to maintain the blind. Subjects in treatment groups 5 and 6 will receive a loading dose consisting of 4 SC injections, and maintenance dosing consisting of 2 SC injections per dose, to maintain the blind. [redacted]

Table 6: Treatment Groups and Dose Regimens



10.1.1. Investigational Product

[redacted]

10.1.2. Placebo

[redacted]

10.2. Study Drug Packaging and Labeling

The final container used for dosing of ISB 830 will be labeled in full regulatory compliance according to the participating country. The label text is translated into the local language. Details on packaging will be provided in the Pharmacy Manual.

10.3. Study Drug Storage

[redacted]

10.4. Study Drug Preparation

Appropriate aseptic technique should be used while preparing and administering the injection. The designated, trained, unblinded pharmacist (or designee) will prepare and dispense study drug for each subject according to the subject's IWRS/IVRS assignment. In special circumstances, (eg, during SARS-CoV-2/COVID-19 pandemic, which may prevent the subject from presenting to the site), an unblinded, qualified healthcare provider may prepare study drug for injection (see Section 10.5).

Detailed instructions will be provided in the pharmacy manual.

10.5. Administration

The day of administration of the first dose of study drug (ISB 830 or placebo) is considered Day 1.

Appropriate aseptic technique should be used while preparing and administering injections. Designated, trained, unblinded personnel (pharmacist or designee) will administer prepared study drug (see Section 10.4) to maintain the blind. The monitoring following dosing will be conducted by blinded study personnel.

In special circumstances, (eg, during SARS-CoV-2/COVID-19 pandemic, which may prevent the subject from presenting to the site), subjects may receive 'at home' dosing, performed by an unblinded, qualified healthcare provider (if such service is available at the time and where permitted by local regulations) who will perform vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [per minute] and oral or tympanic temperature [degrees in Celsius]) by standard methods prior to dosing, and who

will conduct the protocol-specified observation post-injection. Women of childbearing potential will also be administered a monthly urine pregnancy test by the unblinded, qualified healthcare provider, and must have a negative pregnancy result prior to dosing.

Additional details will be provided in the pharmacy manual and in a separate home healthcare provider manual.

Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas), upper thighs, and upper arms, so that the same site is not injected for 2 consecutive dosing visits for doses requiring only a single injection. For doses involving more than a single injection, if it is not possible to alternate quadrants, a different site within the same quadrant may be used as long as areas of erythema and induration are avoided (injection sites should be at least 2-3 cm apart for consecutive dosing visits). To allow for adequate assessment of possible ISRs, study drug should be administered only into areas of normal-looking skin.

As with any antibody/medication, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

10.6. Study Drug Accountability

The designated unblinded pharmacist (or designee) is responsible for study drug (ISB 830 or placebo) accountability at the clinical site and its documentation. Preparation, dispensing and recording of study drug is to done only by authorized unblinded personnel. A designated unblinded clinical study monitor will perform drug accountability at the site. The study drug records must be readily available for inspection by the unblinded clinical study monitor and/or auditor/regulatory agency personnel.

Detailed instructions will be provided in the pharmacy manual.

10.7. Study Drug Handling and Disposal

No medication (new or used) can be returned to the Sponsor or disposed of at the clinical study site until the Sponsor's clinical monitor has verified/reconciled the accuracy of the study medication records at the clinical site and indicated whether the medication should be destroyed at the clinical study site or returned to the Sponsor. Detailed instructions including drug return or other disposition details will be provided in the pharmacy manual.

11. ASSESSMENT OF EFFICACY

11.1. Eczema Area and Severity Index

The EASI is a validated measure used in clinical practice and clinical studies to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head/neck, trunk (including

genital area), upper limbs, and lower limbs (including buttocks), and converted to a score of 0 to 6 (Hanifin et al, 2001).

11.2. Investigator's Global Assessment

The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe) as shown in Table 7.

Table 7: Investigator's Global Assessment Scores and Definitions

IGA Score	Definition
0 = Clear	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

11.3. SCORing Atopic Dermatitis Assessment

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and intensity of AD. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The intensity of 6 specific symptoms of AD is assessed using the following scale: absence (0), mild (1), moderate (2), or severe (3), (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of pruritus and sleeplessness is recorded for each symptom by the subject or relative on a visual analogue scale (VAS), where 0 is no pruritus (or sleep-loss) and 10 is the worst imaginable pruritus (or sleep loss), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C (Kunz et al, 1997).

11.4. Pruritus Numerical Rating Scale

For the Pruritus NRS, subjects will respond to the following question, "On a scale of 0 – 10, with 0 being no itch and 10 being the worst itch imaginable, how would you rate your worst degree of itch during the previous 24 hours?" The Pruritus NRS will be assessed and recorded by the subject once per day, in the morning ideally at the same time, and reviewed by study staff at each clinic visit.

Baseline Pruritus NRS average score for maximum itch intensity will be determined based on the average of daily Pruritus NRS scores for maximum itch intensity (the daily score ranges from 0

to 10) during the 7 days immediately preceding) randomization. A minimum of 3 daily scores out of the 7 days is required to calculate the baseline average score. For subjects who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening).

11.5. Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a subject-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "a little," "a lot," and "very much" with corresponding scores of 1, 2, and 3, respectively; "not at all", "not relevant" responses are scored as "0." Totals range from 0 to 30 (ie, from less to more impairment) and a 5-point change from baseline is considered clinically relevant (Finlay and Khan, 1994; Basra et al, 2008).

11.6. Global Individual Signs Score

For the Global Individual Signs Score (GISS), individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria.

11.7. Body Surface Area Involvement of Atopic Dermatitis

Body surface area (BSA) affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.

11.8. Hospital Anxiety Depression Scale

The Hospital Anxiety Depression Scale (HADS) is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond and Snaith, 1983; Herrmann, 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.

11.9. Patient-Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman et al, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.

11.10. EuroQol-5D

The EuroQol-5D (EQ-5D) is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problems" (level 1), "some problems" (level 2), "extreme problems" (level 3). The VAS scale is a 100-point scale with endpoints ranging from 100 – "best imaginable health state" to 0 – "worst imaginable health state".

11.11. Asthma Control Questionnaire-5

The ACQ-5 is a 5-question version of the Juniper ACQ is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of subjects with a medical history of asthma.

11.12. Sino-nasal Outcome Test

The Sino-nasal Outcome Test (SNOT-22) is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life (QOL). The questionnaire will be administered only to the subset of subjects with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, chronic rhinitis/ rhinosinusitis, nasal polyps, allergic rhinitis).

11.13. Patient Global Assessment of Disease

Subjects will rate their overall wellbeing based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent."

11.14. Patient Global Assessment of Treatment

Subjects will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent".

11.15. Assessment of Sick Leave and/or Missed School Days

Subjects who are employed or enrolled in school will be asked to report the number of sick leave and/or missed school days due to atopic dermatitis (eg, vs due to an accident) in the last 4 weeks.

12. PHARMACOKINETIC, IMMUNOGENICITY AND PHARMACODYNAMIC (BIOMARKER), AND ASSESSMENTS

12.1. Pharmacokinetic, Immunogenicity, and Pharmacodynamic (Biomarker) Blood Sampling Time Points and Allowed Windows

All subjects who consent will have PK, PD and immunogenicity blood sampling. An overview of blood sampling time points for the rich PK group, the sparse PK group, biomarkers and immunogenicity assessments is provided in Table 8.

Blood samples will be collected as per routine phlebotomy procedures and at the time points specified below. Blood samples will be collected during the course of the study through an indwelling cannula placed in forearm veins or alternatively, by a fresh clean venipuncture using a disposable sterilized syringe and a needle. The cannulae will be maintained patent as per local practice; heparin should not be used.

The actual sampling time will be recorded in the source documents and electronic case report form (eCRF).

Actual collection times will be used during PK, PD (biomarker) and immunogenicity calculations.

Details of sample collection, processing and storage will be outlined in a separate laboratory manual.

Table 8: Pharmacodynamic (Biomarker), Pharmacokinetic, and Immunogenicity Blood Sampling Time Points

Time Point	Scheduled PD (Biomarker[1]) Blood Sampling	Scheduled Rich PK Group Blood Sampling	Scheduled Sparse PK Group Blood Sampling	Scheduled Immunogenicity Blood Sampling	Allowed Sampling Time Point Window
Blinded Treatment phase					
Screening	X	N/A	N/A	N/A	Screening period
Day 1 Predose (baseline)	X	X	N/A	X	Within 15 min prior to dosing
Day 1 (4 h post Dose 1)	N/A	X	N/A	N/A	±10 min
Day 2 (24 h)	N/A	X	N/A	N/A	±1 h
Day 5 (96 h)	N/A	X	N/A	N/A	±4 h
Day 6 (120 h)	N/A	X	N/A	N/A	±6 h
Day 8 (168 h)	X	X	N/A	N/A	±8 h
Day 15±1 day (336 h); (Predose Dose 2)	X	X	X		Within 15 min prior to dosing
Day 29±1 day (672 h); (Predose Dose 3)	X	X		N/A	Within 15 min prior to dosing
Day 43±1 day (1008 h); (Predose Dose 4)	N/A	X		N/A	Within 15 min prior to dosing
Day 57±1 day (1344 h, (Predose Dose 5)	X	X		X	Within 15 min prior to dosing
Day 71±1 day (1680 h, (Predose Dose 6)	N/A	X		N/A	Within 15 min prior to dosing
Day 85 (2016 h, (Predose Dose 7)	X	X		X	Within 15 min prior to dosing
Day 85 (2020 h)	N/A	X	N/A	N/A	±10 min
Day 86 (2040 h)	N/A	X	N/A	N/A	±1 h
Day 89 (2112 h)	N/A	X	N/A	N/A	±4 h
Day 90 (2136 h)	N/A	X	N/A	N/A	±6 h
Day 92 (2184 h)	N/A	X	N/A	N/A	±8 h
Day 99±1 day (2352 h, Predose Dose 8)	X	X	X	X	Within 15 min prior to dosing

Table 8: Pharmacodynamic (Biomarker), Pharmacokinetic, and Immunogenicity Blood Sampling Time Points (Continued)

Time Point	Scheduled PD (Biomarker[1]) Blood Sampling	Scheduled Rich PK Group Blood Sampling	Scheduled Sparse PK Group Blood Sampling	Scheduled Immunogenicity Blood Sampling	Allowed Sampling Time Point Window
	Open-label Treatment phase				
Day 113±1 day(2688 h), (Predose Dose 1 of Open-Label Phase Treatment[2])	X	X		X	Within 15 min prior dosing
Day 127±2 days (Predose Dose 2)	N/A	X		X	Within 15 min prior dosing
Day 141±2 days (Predose Dose 3)	X	X		X	Within 15 min prior dosing
Day 169±2 days (Predose Dose 5)	X	N/A		N/A	Within 15 min prior dosing
Day 197±2 days (Predose Dose 7)	X	X		X	Within 15 min prior dosing
EOT/Early Discontinuation	N/A	X		X	±2 days
	Follow-up Phase				
12 Week Follow-up/EOS	N/A	X		X	±5 days

EOS = end of study; EOT = end of treatment; h = hours; min = minutes; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetic; vfPBMC = viably frozen peripheral blood mononuclear cells.
Note: All hours shown in column 1 of the table are in relation to the initial blinded treatment dose on Day 1. The first dose in the open-label treatment phase is on Day 113. Subsequent doses are shown in parentheses in the first column of the table (eg predose Dose 2).

[1] Blood samples for biomarker assessments will be collected (see Section 12.4) when and where biomarker sample kits are available. Biomarkers to be analyzed may include but not limited to leukocyte subpopulation cell counts by flow cytometry; cytokines; total IgE; vfPBMC; serum soluble OX40 and OX40 ligand.

[2] For the subset of subjects who have completed the GBR 830-204 study prior to implementation of the open-label protocol amendment, and provide informed consent to participate in the open-label treatment phase of the study, a PK, PD, and immunogenicity sample must be collected within 15 minutes prior to the first dose.

12.2. Pharmacokinetic Assessments

Blood samples (3.5 mL each) will be collected at appropriate time points defined in Table 2, Table 3 and Table 8.

An experimental population PK design will be used for the PK blood sampling. The subjects in the rich PK group and will have additional blood sampling between Days 1 to 8 (Week 1), and Days 85 to 92 (Week 12). Approximately 80 rich PK subjects will be randomized (in a 1:1:1:1 ratio) to treatment Groups 1-4, and approximately 40 rich PK subjects will be randomized (in a 1:1 ratio) to treatment Groups 5 and 6. All subjects not participating in the rich PK group will be

included under the sparse PK group. Blood samples should be collected from rich and sparse PK group subjects according to the respective schedules described in Table 8. The subjects in the sparse PK group will have widespread sampling with fewer time points for each subject, compared to the rich PK subjects.

Details of sample collection, processing and storage will be outlined in a separate laboratory manual. The samples will be shipped to the bioanalytical laboratory, as specified in the laboratory manual. Serum concentrations of ISB 830 will be quantified using a validated enzyme-linked immunosorbent assay (ELISA) method. In the blinded phase of the study, only the serum samples from subjects, belonging to treatment arms that received ISB 830 will be analyzed. In order to enable this, a designated person at the bioanalytical site will be unblinded. In the open-label phase of the study, PK samples from all subjects will be analyzed. All PK samples collected may be used for future exploratory PK analysis. Any extra serum samples collected (and their derivatives) will be destroyed no later than 15 years and be further analyzed to address specific scientific questions related to ISB 830 (or as required by local regulations).

12.3. Immunogenicity Assessments

Blood samples (5 mL each) will be collected from all subjects at appropriate time points defined in Table 2, Table 3 and Table 8, to detect the presence of anti-drug antibodies (ADA) to ISB 830, as per procedures similar to collection of PK samples. Antibodies generated against ISB 830 will be detected and confirmed using a validated electrochemiluminescence immunoassay (ECLIA) method. Details of sample collection, processing and storage and shipment to the bioanalytical laboratory will be outlined in a separate laboratory manual.

12.4. Pharmacodynamic (Biomarker) Assessments

All Subjects consented will provide required blood samples, including plasma, serum, whole blood, viably frozen peripheral blood mononuclear cells (vfPBMCs) and/or cell subsets, as specified at the listed time points in Table 2, Table 3, and Table 8.

These blood samples will be collected at all sites (when and where biomarker sample kits are available). The collection of these samples should be explained to the subject by the study investigator/site staff at the time of written informed consent.

These samples may be used for biomarker research during the trial and/or at future time points, after the study has been completed. Results of this biomarker research will not be provided to the subject, and are not to be used for clinical decision-making, but may be used by the Sponsor to guide future research and/or drug development.

The samples may be used to examine disease activity, autoimmunity/inflammation, ISB 830 mechanism of action, and/or the effect of the study drug(s) on the course of disease. All samples collected (and their derivatives) will be destroyed no later than 15 years after the completion of the study (or as required by local regulations). Details of sample collection, processing, shipping and storage will be provided to the study sites in a separate manual.

12.4.1. Leukocyte Sub-population Cell Counts by Flow Cytometry

Blood samples (8.5 mL each) for vfPBMC and/or cell subsets will be collected at appropriate time points defined in Table 2, Table 3, and Table 8. The details of sample collection, processing and storage will be outlined in the laboratory manual.

12.4.2. Biomarkers in Peripheral Blood

Blood samples (plasma and/or serum) will be collected at appropriate time points defined in Table 2, Table 3, and Table 8. The details of sample collection, processing and storage will be outlined in the laboratory manual.

12.4.3. Total Immunoglobulin E

Subjects with AD often have elevated immunoglobulin E (IgE). Total IgE levels have been found to modestly correlate with AD severity and may be involved in the pathogenesis of the disease. Changes in total IgE reflects not only on AD, but atopy in general. Baseline IgE levels will be assessed for potential predictive value for treatment response. Post-treatment samples will be evaluated for effects of ISB 830 on total IgE. Blood samples will be collected at appropriate time points defined in Table 2, Table 3, and Table 8. Detailed instructions for blood sample collection will be outlined in the laboratory manual.

12.4.4. Serum Soluble OX40 Ligand and Serum Soluble OX40

Blood samples (3.5 mL) for the estimation of soluble OX40L and soluble OX40 in serum will be collected from subjects at the time points specified in Table 2 and Table 8. The details of sample collection, processing and storage will be outlined in the laboratory manual. Serum concentrations of soluble OX40 L and soluble OX40 will be quantified using a suitable analytical method.

12.4.5. Exploratory Photographs

Subjects who agree to participate in the main study, also agree to allow photography of their skin (excluding pictures of the subject's face) during study participation at specified time points as per Table 2 and Table 3. Photographs of the subject's skin (with the exception of the face) may also be taken at additional time points, as per investigator judgment.

The photographs may be used to examine disease activity, autoimmunity/inflammation, ISB 830 mechanism of action, and/or the effect of the study drug(s) on the course of disease.

Details of photograph collection, processing, shipping and storage will be provided to the study sites in a separate manual.

12.4.6. Optional Genetic Research/Pharmacogenomics Assessments

Subjects who provide written consent for Optional Genetic Research agree to provide a blood sample (one sample may be collected at any visit during the study) to evaluate genetic sequences that may be involved in disease activity, inflammation, study drug mechanism of action, PK/metabolism, and/or the effect of the study drug(s) on the course of disease. Subjects may decline this optional research without effect on their participation in the main study.

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

Safety and tolerability of ISB 830 will be assessed, including AEs; SAEs; TEAEs; anaphylactic events; ISRs; vital signs; physical examinations; electrocardiograms (ECGs); and clinical laboratory parameters, as detailed in the Schedule of Assessments (Table 2 and Table 3).

Guidance will be given to the investigator for the criteria to be used to assess anaphylaxis (Sampson et al, 2006), see Section 13.2.1.4. Injection site reactions will be assessed according to the CTCAE v4.03 (CTCAE v4.03, 2010).

Pandemic Related Safety Assessments:

To ensure the ongoing safety of subjects during the pandemic, study subjects who miss or are unable to attend scheduled clinic visits will be contacted by the site via a safety phone call that includes the collection of AEs/SAEs and concomitant medications. This phone call is to be performed for every missed visit that occurs during the pandemic. If the subject meets other criteria, eg, for withdrawal/discontinuation of the study drug, the site is to follow the protocol in regard to those criteria.

Subject withdrawal/discontinuation criteria are outlined in Section 8.3.

In case of premature discontinuation, the reason must be documented. All appropriate assessments should be conducted at the EOT visit. If the withdrawal is due to an AE, the AE should be monitored until it is resolved, stabilizes or has returned to a status that was prior to the AE (see Section 13.4.1).

13.1.1. Demographic/Medical History

Subject demography information will be collected at the Screening visit. Demography information includes date of birth, sex, and race/ethnicity.

Medical and surgical history, current medical conditions and smoking status will be recorded at the Screening visit.

13.1.2. Vital Signs

Examination of vital signs will be performed as designated on the Schedule of Assessments (Table 2 and Table 3).

Vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [per minute] and oral or tympanic temperature [degrees in Celsius]) will be obtained at the visits designated on the Schedule of Assessments (Table 2 and Table 3) by standard methods. Blood pressure and pulse rate will be measured after the subject has been supine for 5 minutes. All blood pressure measurements should be performed on the same arm, as much as possible.

13.1.3. Weight and Height

Body weight (in kg), height (in cm) and body mass index (BMI) will be assessed at the Screening visit. Body weight will be assessed at the final Follow-up visit.

Body mass index will be calculated as weight (in kg)/height (in m^2).

13.1.4. Physical Examination

Physical examinations (comprehensive or symptom directed/targeted examination) will be performed as designated on the Schedule of Assessments (Table 2 and Table 3). A comprehensive physical examination will include head, eyes, ears, nose and throat (HEENT), cardiovascular system, respiratory system, musculoskeletal system, skin (non-atopic dermatitis related), gastrointestinal system, genitourinary system, and a brief neurological examination. Sign/symptom-directed examination might be performed as per the Investigator's discretion.

Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

13.1.5. Electrocardiogram

Electrocardiograms (single 12-lead ECGs) will be obtained as designated on the Schedule of Assessments (Table 2). A central ECG vendor will be used. Subjects must be in a supine or recumbent position for a period of 5 minutes prior to the ECG.

A physician will have to perform a clinical assessment of each 12-lead ECG. PR, QT and corrected QT (QTc) intervals, QRS duration and pulse rate will be recorded. The QT interval will be corrected for pulse rate (QTc) using Fridericia's formula. A copy of the ECG tracing has to be stored as source data.

The following ECG parameters will be recorded: heart rate (HR), RR interval (RR), PR interval, QRS-duration, QT interval, QT interval corrected for HR (QTc) corrected according to Fridericia's formula (QTcF), QTc corrected according to Bazett's formula (QTcB), and the Investigator's conclusion on the ECG profile.

Fridericia's formula (QTcF):

(observed QT interval divided by cube root of RR interval, in seconds)

Bazett's formula (QTcB):

(observed QT interval divided by square root of RR interval, in seconds)

Abnormalities in an ECG will be assessed as "clinically significant" or "not clinically significant."

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 13.2.1).

For ECG abnormalities meeting criteria of an SAE (see Section 13.2.1.3, the site must fax or email the SAE report including the ECG report (with Subject ID only, and subject's name masked) to the Sponsor using the SAE form (see Regulatory Reporting Requirements for SAEs [see Section 13.5]).

13.1.6. Laboratory Assessments

A list of the clinical laboratory tests to be performed is included in Appendix 1, Table 11. The Schedule of Assessments (Table 2 and Table 3) show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Subjects should be in a seated or supine position during blood collection.

A central laboratory should usually be used to measure laboratory parameters that are to be assessed as part of the safety analyses for the Clinical Study Report (CSR). Local laboratories may be used in cases of a safety concern during the study, in which case the blood sample would be split (or 2 samples collected) to allow both a local laboratory and a central laboratory analysis. In such cases, the local laboratory result(s) will be considered part of the source documentation only and the central laboratory result will be entered into the clinical database. Local laboratory reports from non-split samples generated to follow safety concerns will be contained in the source documentation.

Any abnormal clinical laboratory test results (hematology, blood chemistry, or urinalysis) that worsen from baseline and considered to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

13.1.6.1. Virus Serology

Serology will be performed for HBsAg, anti-HBcAg, anti-HCV, and HIV at screening only.

13.1.6.2. Pregnancy Testing

For women of childbearing potential (WOCBP), a urine pregnancy test may be performed at the initial screening visit, at the Investigator's discretion. Serum beta-human chorionic gonadotropin (β-HCG) is required within 7 days prior to randomization and at the end of study follow-up visit; all other visits may be urine pregnancy tests. The pregnancy test on Day 1 must be negative prior to randomization. If a serum pregnancy test is performed on Day 1, it is not necessary to perform a urine pregnancy test the same day.

For postmenopausal women only, FSH screening will be performed at screening to confirm non-childbearing potential (FSH ≥40 IU/L).

FSH testing, and serum pregnancy and urine pregnancy testing will be performed by a central laboratory. Screening pregnancy testing required within 7 days prior to randomization, will be performed by a central laboratory and may be performed by a local laboratory if timing necessitates.

13.1.6.3. Confirmation of Medical Care by Another Physician

The Investigator will instruct subjects to inform clinical site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the Investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

13.1.7. Estimate of Volume of Blood to be Collected

The estimated amount of blood to be collected for clinical safety lab tests including pregnancy testing and FSH testing is 7 mL per visit, the estimated amount of blood to be collected for each PK blood draw per visit is 3.5 mL and the estimated amount of blood to be collected for each immunogenicity blood draw is 5 mL. The estimated amount of blood to be collected for each biomarker analysis is 23.5 mL, including blood for vfPBMCs.

The total maximum amount of blood that may be collected per subject in the study, including all safety labs, immunogenicity, rich PK and biomarker samples, and optional PG blood sample over 70 weeks is approximately 538 mL.

13.2. Adverse and Serious Adverse Events

The Investigator or site staff will be responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

The reference safety information for this study is the current GBR 830/ISB 830 IB.

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of the study drug, whether or not related to the study drug. An AE includes any event, regardless of the presumed causality between the event and the study drug.

Events that, while not necessarily meeting the definition of AEs, should be treated as such because they may be reportable to Regulatory Authorities according to AE reporting regulations, whether or not considered causally associated with IP, include the following:

- Study drug overdose, whether accidental or intentional.
- Study drug abuse.
- An event occurring from study drug withdrawal.
- Any failure of expected pharmacological action.
- Inadvertent or accidental study drug exposure (eg, product leaking or being spilled onto a subject or care-giver).
- Medication errors (ie, incorrect route of administration, incorrect dosage, use of incorrect product).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Note that significant worsening of symptoms (ie, requiring systemic steroids, antibiotics, or hospitalization) will be reported as an AE. For guidance on hospitalization, including planned hospitalization, emergency department visits, and prolongation of existing hospitalization, please refer to Section 13.2.1.3.

13.2.1.2. Assessment of Severity of Adverse Events

The severity of AEs is classified (Table 9) according to the CTCAE v4.03 that was published 14-Jun-2010 by the US Department of Health and Human Services (National Institutes of Health [NIH] and National Cancer Institute [NCI]).

Table 9: Classification of Severity of Adverse Events (CTCAE v4.03)

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 activities of daily living[1] (ADL).
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
Grade 4	Life-threatening	Urgent intervention indicated.
Grade 5	Death	Death related to AE.

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
[1] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Source: CTCAE v4.03, 2010

The criteria for assessing severity are different from those used for seriousness (see Serious Adverse Events [see Section 13.2.1.3] for the definition of an SAE).

13.2.1.3. Serious Adverse Events

A SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  - NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- May result in inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as any inpatient admission (even if less than 24 hours). Inpatient admission does not include the following:
  - Emergency Room department visits
  - Outpatient/same day/ambulatory procedures/observation/short-stay units
  - Hospice facilities/respite care
  - Rehabilitation facilities
  - NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- A hospitalization planned prior to study enrollment is to be considered a therapeutic intervention and not the result of a new SAE. If the planned hospitalization or procedure is executed as planned, it will be recorded in the subject's medical history or procedures. However, if the event/condition worsens during the study, it must be reported as an AE.
- Emergency room visits that do not result in a hospital admission should be evaluated for one of the other serious outcomes (eg, life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Results in disability/incapacity
  - NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or

malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

13.2.1.4. Clinical Criteria for Diagnosing Anaphylaxis

Clinical criteria to be used for diagnosing anaphylaxis (Sampson et al, 2006) are shown in Table 10. The Investigator should also use these criteria when reporting the event.

Table 10: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:	
1.	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2.	Two or more of the following that occur rapidly after exposure *to a likely allergen* for that subject (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3.	Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

BP = blood pressure; PEF = peak expiratory flow.
*Low systolic blood pressure for children is defined as: less than 70 mm Hg from 1 month to 1 year; less than (70 mm Hg + [2 x age]) from 1 to 10 years; and less than 90 mm Hg from 11 to 17 years.
Source: (Sampson et al, 2006), Table 1.

13.3. Relationship to Study Drug

The relationship of AEs to study medication is classified as follows:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event

- The presence of non-study treatment-related factors that are known to be associated with the occurrence of the event.

For each AE, the Investigator should answer the following question with Yes or No:

- Was there a reasonable possibility (evidence) that the drug caused the AE?
  - A reasonable possibility means that there are facts (evidence) or arguments to suggest a causal relationship.
  - NOTE: For subjects who have not started receiving study medication, or run-in phase medications, the answer must be no.

13.4. Recording Adverse Events

13.4.1. Collection of Adverse Events

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of signing the ICF until the final Follow-up visit.

SAEs will be collected over the same time period as stated above for AEs. Any SAEs assessed as related to study participation (eg, study drug, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a concomitant medication that is a Ichnos Sciences product, will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to the Sponsor within 24 hours, as indicated in Section 13.5.

The Investigator will enquire about the occurrence of AEs/SAEs at every visit throughout the study (including Follow-up and Early Withdrawal visits where applicable), by asking the following non-leading verbal question of the subject (or care-giver, where appropriate):

- "Have you had any medical problems since your last visit?"

All AEs not resolved by the end of the study or that have not resolved upon the subject's discontinuation in the study must be followed until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

13.4.2. Recording of Adverse Events

All AEs, regardless of the seriousness, severity or relationship to the study medication must be recorded on the AE eCRF.

Adverse events that meet the definition of an SAE must be reported on the SAE Form provided for this study.

Adverse events must be documented in clear, unambiguous medical language. Do not use abbreviations or acronyms.

For each AE record only the diagnosis, do not report the characteristic signs and symptoms of the diagnosis as additional AEs.

If a diagnosis is not available record each sign and symptom as an AE, when a diagnosis becomes available, update the AE eCRF, to record the relevant diagnosis only.

In general, abnormal findings at screening should be recorded in the subject's Medical History or in the Concurrent Conditions section in the eCRF. However, if in the Investigators opinion, the finding is clinically significant and represents a condition that was not present at signing of informed consent, then the finding must be reported as an AE.

13.5. Reporting Adverse Events

Prompt notification of SAEs by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigators.

All SAEs must be reported to the Sponsor immediately or within 24 hours of the Investigator or their staff becoming aware of them. Reporting should be performed by recording as much information as is available at the time on the SAE Form and sending it to the contact information provided below:

[redacted]

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information. Follow-up reports must be submitted to the Sponsor until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available.

Additional information will be requested by the Sponsor as necessary.

13.5.1. Pregnancy

The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any pregnancy that occurs during study participation must be reported to the Sponsor, using a clinical trial pregnancy form, immediately or within 24 hours of the Investigator learning of its occurrence. The report should contain as much information as possible and should be sent to:

[redacted]

[redacted]

When further information becomes available, the Pregnancy Report Form should be updated with all new information and reported immediately via the same contact information above. The Pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, and this information must be sent to the Sponsor as above. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Additional information will be requested by the Sponsor as necessary.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study drug, must be promptly reported to the Sponsor.

14. TIMING OF STUDY ASSESSMENTS

Study procedures and assessments are summarized across all study visits within the Schedule of Assessments (Table 2 and Table 3). Pharmacokinetic, immunogenicity, and biomarker blood sampling time points and allowed windows are described in Table 8.

Patient reported assessments should be completed before investigator assessments. If assessments are planned for the same scheme time, the order of the assessments should be performed in the following order: vital signs, ECG, PK and immunogenicity blood sampling, AD photography, and study drug dosing. PK blood sampling should occur exactly on time. Samples collected outside the window period will be reported as protocol deviations. Irrespective of whether the PK samples were collected within the allowed window period or outside the allowed window period, the actual time point of sampling will be recorded (in the eCRF) and this time point will be used for the calculation of PK parameters.

Blood samples will be collected as per routine phlebotomy procedures at time points specified in Table 2, Table 3, and Table 8.

14.1. Screening Period (Day -28 to Day -1)

Screening should be conducted within the 28 days before the randomization to study treatment (Day 1). Before performing any procedures or assessments, the nature of the study and the potential risks associated with the study must be explained to all subjects and written informed consent must be obtained.

An electronic subject diary device will be given to each subject at the screening visit. The subject will be trained on the use of the device. This device will be used for the Pruritus NRS scale and other observations required for screening (see Table 2, Schedule of Assessments). The subject will be instructed to enter the data every morning at a designated time and how to record them. A minimum of 3 days of diary must be recorded in the week prior to randomization. The subject must enter data into the electronic subject diary every day from start of screening period to Day 113 (Week 16).

Once informed consent for the study (and Health Insurance Portability and Accountability Act [HIPAA] authorization or other locally required documentation, as applicable) has been

obtained, procedures and evaluations listed in Schedule of Assessment (SoA, Table 2 and Table 3) will be performed.

At the discretion of the Investigator, 1 re-test will be allowed at screening for laboratory investigations other than viral serology, to confirm findings for clinical conditions that are considered to be acute, reversible, and non-serious.

Subjects who have completed the study or are in follow-up at the time the open-label protocol amendment is implemented and provide written informed consent to participate in the open-label treatment phase of the study, will undergo a modified screening visit which includes, Informed Consent, Medical History, Inclusion/Exclusion Criteria (with the exception of Inclusion Criteria 5, 6, 7, 8, 9, 10 and Exclusion Criteria 1 and 5), Prior and Concomitant Medication Evaluation, Vital Signs, Physical Examination (Comprehensive), Weight, 12-Lead ECG, Clinical Laboratory Assessments, Serology, TB Testing, Urine Pregnancy Test, ACQ-5, Immunogenicity blood samples, PK blood samples IGA/EASI (Investigator completed), and Adverse Event Assessment.

14.2. Treatment Period

At each visit, the procedures and evaluations described for the visit in the SoA are to be performed (Table 2 and Table 3).

14.2.1. Blinded Treatment Phase

The blinded treatment phase consists of following visits.

- Day 1 (Baseline and Randomization)
- Day 2 to Day 6 (Rich PK Group): Blood samples will be collected as per routine phlebotomy procedures and at time points specified in Table 2 and Table 8.
- Non-Dosing Day Visits: Day 8 (Week 1)
- Dosing Days: Day 15±1 (Week 2), Day 29±1 (Week 4), Day 43±1 (Week 6), Day 57±1 (Week 8), Day 71±1 (Week 10), Day 85 (Week 12), Day 99±1 (week 14)
- Days 85 (Week 12) to Day 92 (Week 13) (Rich PK Group only)
- Blinded End of Treatment/Early Discontinuation: Day 113±1 (Week 16)

14.2.2. Start of Open-label Treatment Phase: Day 113

All blinded EOT treatment phase assessments must be completed prior to open-label treatment dosing.

Note: The subset of subjects who have completed the GBR 830-204 study prior to implementation of the open-label protocol amendment and provide informed consent to participate in the open-label treatment phase of the study, will undergo the modified screening assessments on Day 113.

Modified Screening Visit includes informed consent, medical history, eligibility for inclusion/exclusion criteria (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10, and exclusion criteria 1 and 5), prior and concomitant medications, vital signs, comprehensive

physical examination, weight, 12-Lead ECG, clinical laboratory, serology, TB testing, urine pregnancy test, ACQ-5, IGA/EASI (Investigator completed), and adverse event assessment.

On the Week 16 (Day 113) visit, the following assessments must be completed prior to study drug administration: prior and concomitant medications, vital signs, physical examination (comprehensive or targeted), clinical laboratory, urine pregnancy test, immunogenicity blood samples, PK blood samples, IGA/EASI (Investigator Completed), ACQ-5, adverse events assessment.

14.2.3. Open-label Treatment Phase/Long-term Assessments

The open-label treatment phase consists of the following visits:

- Dosing Days: Day 113 (Week 16) to Day 364 (Week 52): The window period for each visit during this period is ±2 days except the visit on Day 113±1.
- Open-label End of Treatment Phase/Early Discontinuation: Day 379 (Week 54)

14.3. Follow-up Period: Week 58, Week 62 and Week 66

The follow up period will consist of a phone call 4 weeks and 8 weeks, and a final 12 week follow up clinic visit after last EOT.

Weeks 58 and 62 will be phone contacts only. Week 66 will be an in-person clinic visit.

Refer to Section 8.3 if at any time point a subject is withdrawn from the study. In the event of early withdrawal, assessments will be performed as soon as possible after a subject withdraws from the study. A subject, who has completed blinded or open-label study drug treatment, will be asked to complete all procedures scheduled for the EOT visits at time of completion (Day 113 [Week 16], or Day 379 [Week 54], respectively). The subject should continue to the follow-up period for a phone call 4 weeks and 8 weeks after the EOT visit and a final follow up visit 12 weeks after the EOT visit, unless the subject withdraws consent or is lost to follow-up.

After the end of participation in the study, the subject will be treated, as needed, at the discretion of the Investigator. Every effort should be made to contact the subject for a follow-up if the subject has not returned to the clinic for scheduled visits (lost-to-follow-up subject) to ensure the safety of the subject.

15. STATISTICS

The Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP will be finalized before the database lock at the latest. If there are differences, the information in the SAP will supersede the information in the protocol. Any changes from the analyses planned in the SAP will be justified in the CSR.

All analyses will be performed by the Sponsor (or designee Contract Research Organization [CRO]) using SAS® software program version 9.3 or above. In general, all data will be summarized with descriptive statistics (number of subjects, mean, and standard deviation [SD],

minimum, median, and maximum) for continuous variables and frequency and percentage for categorical variables.

15.1. Sample Size

15.2. Analysis Sets

15.2.1. Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who are randomized and received at least 1 dose of study medication. Based on the intent-to-treat principle, subjects will be analyzed according to the treatment group assigned.

15.2.2. Per Protocol Set

The Per Protocol Set (PPS) consists of all FAS subjects who have no major protocol deviations of eligibility or on-treatment study conduct.

15.2.3. Safety Analysis Set

The Safety Analysis Set (SAS) consists of all subjects who were randomized and took at least 1 dose of study medication. Subjects will be analyzed according to the treatment they received.

15.2.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAS population who received ISB 830 and for whom sufficient serum concentration data are available to facilitate derivation of PK parameters, do not have any major protocol deviation, and for whom the time of dosing and the time of sampling are known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time points from the PKAS will be documented in the SAP.

15.3. Endpoints

15.3.1. Primary Endpoint

- Percentage change from baseline in EASI score at Week 16.

15.3.2. Secondary Endpoint(s)

Efficacy Endpoints:

- Proportion of subjects with EASI-75 (≥75% improvement from baseline) at Week 16.
- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline ≥2 points at Week 16.
- Proportion of subjects with improvement (reduction) of Pruritus Numerical Rating Scale (NRS) ≥4 from baseline to Week 16.
- Proportion of subjects who achieve an EASI-50 (≥50% improvement from baseline) response from baseline through Week 16.
- Change in SCORAD from baseline through Week 16.
- Change in the DLQI from baseline through Week 16.
- Change in GISS (erythema, infiltration/population, excoriations, lichenification) from baseline through Week 16.
- Change in HADS from baseline through Week 16.
- Change in POEM from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Disease from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Treatment from baseline through Week 16.
- Assessment of sick leave and/or missed school days through Week 16.

Safety Endpoints:

- Incidence of TEAEs from baseline through Week 16 and Week 54.
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of conjunctivitis TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of treatment-emergent SAEs from baseline through Week 16 and Week 54.
- Incidence of TEAEs leading to treatment discontinuation from baseline through Week 16 and Week 54.
- Overall number of TEAEs and SAEs through Week 16 and Week 54.
- Vital signs, clinical laboratory values, and ECG results monitored from baseline through Week 16 and Week 54.
- Formation of ADA to ISB 830 to evaluate immunogenicity.

Pharmacokinetics Endpoints:

- C_{max}, t_{max}, $AUC_{0\text{-}tau}$, AUC from time 0 to the last measurable concentration ($AUC_{0\text{-}t}$), and other related parameters will be estimated using data from the rich PK group from the blinded treatment phase. C_{trough} values will be estimated using data from both rich and sparse PK groups from the blinded treatment phase.

15.3.3. Exploratory Endpoints

Samples for exploratory biomarker endpoints will be collected when and where biomarker sample kits are available.

Exploratory biomarker endpoints are:

- Messenger RNA (mRNA) expression of immune and barrier measures in skin biopsies at baseline, end of Week 8, and end of Week 16.
- Biomarker analysis in ISB 830 responder and non-responder populations, to evaluate the relationship of biomarkers with clinical efficacy measures.
- Assays on plasma, serum, viably frozen peripheral blood mononuclear cells (vfPBMCs) and/or cell subsets/derivatives.

Exploratory efficacy endpoints are:

- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points through Week 54.
- Proportion of subjects with EASI-75 (≥75% improvement from baseline) through Week 54.
- Proportion of subjects who achieve an EASI 50 (≥50% improvement from baseline) through Week 54.
- Change in the EQ-5D through Week 16.
- Change in Juniper ACQ-5 from baseline through Week 16.
- Change in the SNOT-22 from baseline through Week 16.
- To assess qualitative changes in Photographs of skin lesions taken at time points specified in the SoA (Table 2 and Table 3).

15.4. Subject Disposition

Data on subject disposition (number of subjects enrolled, number of drop-outs, and reasons for drop-out), demographics (gender, age, height), and other baseline characteristics will be summarized. The safety, tolerability, PK, and other data from the study will be listed and summarized descriptively by treatment. The number (percentage) of subjects who were screened for the study (enrolled subjects, ie, those who signed informed consent) and reasons for screen failure will be described.

15.5. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the FAS. Descriptive statistics will include number of subjects, mean, SD, minimum, median and maximum for continuous variables, and frequency and percentage for categorical variables. Continuous demographic and baseline variables include age, height and body weight, and BMI; categorical variables include gender, race, and ethnicity.

15.6. Efficacy Analyses

The primary efficacy analysis will be the percentage change from baseline in EASI score, and the secondary efficacy analysis will be the IGA and EASI 75 (subjects achieving 75% reduction from baseline in EASI score). The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The EASI and IGA scores will be assessed at time points described in the Schedule of Assessments.

The primary efficacy analyses will be conducted for all subjects in the FAS using the treatment arm as assigned. In addition, the efficacy analyses for the primary endpoint and secondary endpoints (IGA, EASI-75) will be conducted using the PPS.

For both Part 1 and Part 2 of the study, the primary endpoint (percentage change from baseline in EASI score at Week 16) will be analyzed using a MMRM model. The model will adjust for study treatment, baseline, randomization stratification factors, visit as well as baseline-by-visit and treatment-by-visit interactions.

The continuous secondary endpoints will be analyzed using the MMRM model as performed for the primary endpoint.

The Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity) will be used to analyze the categorical secondary endpoints.

To test the robustness of the MMRM model for the primary endpoint, sensitivity analyses using tipping point approach will be conducted. In addition, the primary endpoint will be analyzed using the complete dataset (subjects who complete the week 16 and had EASI measurement).

For Part 2 of the study, Group 5 ([redacted] loading [redacted] q2w maintenance) will be compared to the corresponding placebo arm (Group 6) using the same statistical methods used in the analysis of the first part of the study.

To assess the robustness of the results in the Part 2 of the study, the analyses on primary endpoint and secondary endpoints (IGA, EASI-75) will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

Parts 1 and 2 are two independent parts of the study protocol and will therefore be analyzed separately. That is, upon completion of the double-blind period of Part 1, the database will be partially locked. The data will be analyzed and the topline results (TLR) determined.

Similar activities will take place upon the completion of the double-blind period of Part 2.

The efficacy results from these 2 parts of the study will be kept separate. However, the safety results will be presented side-by-side.

Details of efficacy, safety and PK analyses will be specified in the GBR 830-204 Statistical Analysis Plan (SAP) and included in the Clinical Study Report (CSR). Population pharmacokinetic and exposure-response modeling will be described in a Modeling Plan and data will be published in a separate report.

Biomarker analyses will not be part of the CSR and will be described separately.

Detailed statistical methods, including methods for the handling of missing data for analyzing the secondary and exploratory endpoints a will be described in the SAP.

15.7. Pharmacokinetic, Pharmacodynamic (Biomarker), and Immunogenicity Analyses

15.7.1. Pharmacokinetic Analyses

The PKAS will be used for the PK analyses. The PK parameters will be derived for individual subject by non-compartmental analysis using appropriate validated software. Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, and other related parameters) will be estimated based on data from the rich PK group from the blinded treatment phase.

Estimates of C_{trough} will be derived using the data from both rich PK group and sparse PK group from the blinded treatment phase.

The PK parameters will be summarized in tabular and graphic form. Details of the PK analysis will be specified in the SAP.

The serum concentration data from both rich and sparse PK group may be used for the population PK and exposure-response analysis and will be reported separately.

15.7.2. Immunogenicity Analyses

The number and percent incidence of positive and negative ADA status of subjects by treatment, and time points will be provided. Titers and neutralizing potential of confirmed positive samples will be reported. Details will be provided in the SAP.

15.7.3. Pharmacodynamic (Biomarker) Analyses

Summary statistics will be provided for PD biomarkers. Biomarker analyses will not be part of the CSR and will be described separately.

15.8. Safety Analyses

All safety analyses will be performed on the SAS population, according to the actual treatment received. Adverse events will be summarized by system organ class and preferred term. Subjects will be counted only once for each preferred term, system organ class, and by the highest severity of an event. Laboratory evaluations will be summarized with descriptive statistics at each visit, and change from baseline summarized for each post-baseline visit. Laboratory measurements will also be summarized based on the number and percentage of subjects above or below a pre-specified threshold for each test. Details will be presented in the SAP.

15.8.1. Extent of Exposure

The duration of exposure to study drug will be summarized separately by respective treatment group for SAS subjects.

15.8.2. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to investigational product will be summarized by system organ class, preferred term and treatment group. Subjects will be counted only once for each preferred term, system organ class, and by the highest severity of an event. The number and percentage of AEs by severity will also be summarized. All AEs will be displayed in listings.

15.8.3. Laboratory Values

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts in laboratory tests relative to reference ranges from baseline to the worst post-baseline value during treatment will also be tabulated. All laboratory data will be displayed in listings.

15.8.4. Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time. Values of potential clinical significance will be tabulated. All vital signs data will be displayed in listings.

Shift tables will present changes from baseline (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

15.8.5. Electrocardiograms

The absolute values and the change from baseline for ECG parameters will be summarized. An outlier analysis of ECG results will be conducted.

All ECG variables will be presented by visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

15.8.6. Physical Examination

Descriptive statistics will be used to summarize findings of potential clinical significance and will be listed.

15.9. Interim Analysis

No interim analyses are planned for this study.

15.10. Data Safety Monitoring Board

This study will institute a data safety monitoring board (DSMB) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DSMB will be constituted prior to the randomization of the first subject. The DSMB will monitor subject safety by formally reviewing accumulated safety data by treatment group at least twice during the study, but may require additional review as per DSMB charter. This includes but does not limit the role of the DSMB to evaluate these data and to provide recommendations to the sponsor to continue or modify the follow-up phase of the study as outlined in the DSMB charter.

It is expected that the DSMB will consist at a minimum of 2 physicians with appropriate disease area qualifications and 1 statistician. There will be a meeting with the DSMB describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DSMB charter.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator or other staff needs information or advice.

16.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

16.2.1. Inspection

An inspection is defined as the act of a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsor's and/or CRO facilities or any other establishments deemed appropriate by the regulatory authorities.

16.2.2. Audit

An audit is a systematic and independent review of study-related activities and documents to determine whether study-related activities were conducted and the data were accurately recorded and analyzed according to the protocol, standard operating procedures, Good Clinical Practice (GCP), and the appropriate requirements.

In conducting this study, the Investigator accepts that the Sponsor, IRB/IEC or regulatory body may, at any time by appointment, conduct an audit of the study site.

16.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the clinical study. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising

used to recruit subjects for the study, as well as any materials (eg diaries, questionnaires) to be given to subjects. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/GCP guidelines, applicable regulatory requirements and the Sponsor's policy on Bioethics.

18.3. Written Informed Consent

The Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The Investigator is responsible for obtaining informed consent from each subject/legally acceptable representative (LAR) participating in the study. All pertinent aspects of the study must be explained to the subject/LAR before he or she signs the informed consent. The subject's signed and dated informed consent must be obtained before conducting any study procedures.

Informed consent must be obtained from the subject/LAR before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic screening procedures and the administration of the first dose of the study medication. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject/LAR should understand the statement before signing and dating it and will be given a copy of the signed document.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

19. DATA HANDLING AND RECORD KEEPING

19.1. Data Collection

Clinical data will be entered by authorized site personnel into a 21 CFR Part 11 compliant electronic data capture system. All clinical data relating to the study will be recorded on the

eCRF unless transmitted to the Sponsor or designee electronically (eg, central laboratory data). The Investigator must maintain source documents that support the information entered in the eCRF. Study monitors will perform ongoing source data verification to ensure that data entered into the eCRF by authorized site personnel are consistent with the source documents. The Investigator is responsible for confirming data entries are complete and accurate by physically or electronically signing the eCRF. The Sponsor or designee is responsible for the data management of the study, including quality-check of the data.

19.2. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

19.3. Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

19.4. Financing and Insurance

The Sponsor will provide clinical study insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

20. PUBLICATION POLICY

The Sponsor recognizes and supports the publication and dissemination of scientific information as a means of furthering knowledge. The general strategy regarding publication of the study (what, when, where, etc.) will be mutually agreed upon by the Investigator and Sponsor. However, in order to protect its commercial interests, the Sponsor reserves the right to manage the publication of all study results. The Investigator agrees that oral and written communication to third parties of any procedures or results from the study is subject to prior written consent of the Sponsor. Presentation material and/or manuscript(s) for publication will be reviewed by Sponsor prior to submission for publication. This review will be completed within 30 days of receiving presentation material and 60 days of receiving the manuscript from the Investigator. Alterations in the material will only be made in agreement between the Investigator and the Sponsor.

In the event of inconsistency between the above and the study contract, the terms of the study contract would prevail to the extent of such inconsistency.

21. LIST OF REFERENCES

1. Basra MK, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol 2008;159(5):997-1035.
2. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol 2004;140(12):1513-9.
3. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Pulishded June 14, 2010.
4. Croft, M. Control of immunity by the TNFR-related molecule OX40 (CD134). Annu Rev Immunol 2010;28:57-78.
5. Deckers IA, McLean S, Linssen S, Mommers M, van Schaych CP, Sheikh A. Investigating International Time Trends in the Incidence and Prevalence of Atopic Eczema 1990–2010: A Systematic Review of Epidemiological Studies 2012. PLoS ONE 7(7): e39803. https://doi.org/10.1371/journal.pone.0039803
6. Eckert L, Gupta S, Amand C, Gadkari, A, Mahajan P, Gelfand J. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. J Am Acad Dermatol 2017;77:274-9.
7. Eckert L, Gupta S, Amand C, Gadkari, A, Mahajan P, Gelfand J. The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. J Am Acad Dermatol 2018, 78(1):54-61.
8. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: Part 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70(2):338-51.
9. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210-6.
10. FDA Guidance for Industry M3(R2). Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, Rev 1, Jan 2010. Available at: https://www.fda.gov/downloads/drugs/guidances/ucm073246.pdf.
11. 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;10(1):11-8.
12. Herrmann C. International experiences with the hospital anxiety and depression scale- a review of validation data and clinical results. J Psychosom Res 1997;42(1):17-41.
13. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonized tripartite guideline: general considerations for clinical trials, E8. CPMP/ICH/291/95, Jul 1997. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf

14. International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonized tripartite guideline: Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, M3(R2). CPMP/ICH/286/95, Jun 2009. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf
15. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J,Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997;195(1):10-9.
16. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391-7.
17. Seshasayee D, Lee WP, Zhou M, Shu J, Suto E, Zhang J, et al. In vivo blockade of OX40 ligand inhibits thymic stromal lymphopoietin driven atopic inflammation. J Clin Invest 2007;117(12):3868-78.
18. Webb GJ, Hirschfield GM, Lane PJ. OX40, OX40L and autoimmunity: a comprehensive review. Clin Rev Allergy Immunol 2016;50(3):312-32.
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-70.

APPENDIX 1. CLINICAL LABORATORY TESTS

The following tests will be performed. Clinical evaluation of all clinical laboratory data will be performed by a qualified physician. Reference range values from the central lab will be used for the tests mentioned below.

Table 11: Clinical Laboratory Tests

<table>
<tr><td>HEMATOLOGY
Hemoglobin
Hematocrit
White blood cell count (total and differential, in absolutes and percentages)
Red blood cell count with mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC)
Platelets
Circulating eosinophil counts</td><td colspan="2" rowspan="2">SERUM BIOCHEMISTRY
Electrolytes
Sodium
Potassium
Calcium
Chloride
Bicarbonate
Liver function tests
Total and direct bilirubin
Total protein
Globulin
Albumin
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma-glutamyl transferase (GGT)
Alkaline phosphatase (ALP)
Lactate dehydrogenase (LDH)</td><td rowspan="2">Renal function tests
Serum creatinine
Blood urea nitrogen (BUN)
Other
Serum glucose
Serum follicle-stimulating hormone (FSH) (postmenopausal women, only at screening)
Serum and urine beta-human chorionic gonadotropin (HCG) (for women of childbearing potential [WOCBP] only)
Serum immunoglobulins
Lipid Profile
Total cholesterol
Triglycerides
High density lipoprotein (HDL)
Low density lipoprotein (LDL)
Very low-density lipoprotein (VLDL)</td></tr>
<tr><td>URINALYSIS
pH
Specific gravity
Glucose
Protein
Ketones
Occult blood
Bilirubin
Leukocyte esterase
Nitrite
Routine microscopy including WBC/HPF and RBC/HPF</td></tr>
<tr><td>SEROLOGY
Hepatitis B (HBsAg)
Anti-hepatitis B core antigen (Anti-HBcAg)
Hepatitis C antibody (anti-HCV)
Human immunodeficiency virus (HIV-1 and -2)</td><td colspan="3">OTHER
QuantiFERON Gold Blood TB Test
Total IgE</td></tr>
</table>

APPENDIX 2. LIST OF CONTACT DETAILS

Additional information and contact details related to the study will be provided to each clinical site separately in relevant documents and procedural manuals.

Medical Monitor (Ichnos Sciences):

Medical Monitor (CRO):
Information will provided separately from the protocol.

APPENDIX 3. SUMMARY OF CHANGES IN CURRENT PROTOCOL AMENDMENT

PROTOCOL NUMBER: GBR 830-204

PROTOCOL AMENDMENT 9

SUMMARY OF CHANGES

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of GBR 830 in Adult Subjects with Moderate to Severe Atopic Dermatitis

PROTOCOL HISTORY

PROTOCOL VERSION 1.0, 20-Mar-2018

PROTOCOL VERSION 2.0, (AMENDMENT 1), 06-Apr-2018

PROTOCOL VERSION 3.0, (AMENDMENT 2), 07-Nov-2018

PROTOCOL VERSION 4.0, (Non-substantial AMENDMENT 3), 29-Nov-2018

PROTOCOL VERSION 5.0, (Germany AMENDMENT 4), 08-Jan-2019

Note: Version 3.0 (Global Amendment 2), and Version 4.0 (Global Amendment 3) are not applicable to Germany

PROTOCOL VERSION 6.0, (Czech Republic AMENDMENT 5), 16-Jan-2019

Note: Version 3.0, (Global Amendment 2), Version 4.0, (Global Amendment 3), and Version 5 (Germany Amendment 4) are not applicable to Czech Republic

PROTOCOL VERSION 7.0, (Germany and Czech Republic AMENDMENT 6), 26-Feb-2019

PROTOCOL VERSION 8.0, (Global AMENDMENT 7), 26-Jun-2019

PROTOCOL VERSION 9.0, (AMENDMENT 8), 28-Jan-2020

PROTOCOL VERSION 10.0, (AMENDMENT 9), 05-May-2020

Description of Changes in Protocol Version 10.0 (Amendment 9) dated 05-May-2020

Minor editorial changes for accuracy, clarity, and consistency have been made throughout the document and are not included in the description(s) below.

Key: **Bold:** Newly added text

~~Strikethrough text~~: Deleted text from the previous version of the protocol.

A. Details of Substantial Changes to the Protocol, from Version 9.0, Amendment 8 to Protocol Version 10.0, Amendment 9

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
1. Synopsis, Section 7.1.4 Number of Subjects (Planned)		
Used to read: For Groups 1 through 4, a sufficient number of subjects will be screened to randomize 312 eligible subjects in a 1:1:1:1 ratio. For Group 5 and 6, a sufficient number of subjects will be screened to randomize 156 eligible subjects in a 1:1 ratio to either ISB 830 or Placebo, therefore a total of 468 subjects are planned to be randomized in this study. The randomization will be stratified by disease severity (moderate or severe, as assessed by IGA), geographic region (North America vs European Union), and subjects consenting to rich PK sampling (Yes/No).	Now reads: For Groups 1 through 4, a sufficient number of subjects will be screened to randomize 312 eligible subjects in a 1:1:1:1 ratio. For Group 5 and 6, a sufficient number of subjects will be screened to randomize 156 eligible subjects in a 1:1 ratio to either ISB 830 or Placebo, therefore ~~a total of~~ **approximately** 468 subjects are planned to be randomized in this study. The randomization will be stratified by disease severity (moderate or severe, as assessed by IGA), geographic region (North America vs European Union), and subjects consenting to rich PK sampling (Yes/No). **The actual number of subjects randomized in Groups 5 and 6 may be different than initially planned due to the impact of the SARS-CoV-2/COVID-19 pandemic (see Section 8.3.4).**	Enrollment of additional subjects is now allowed due to pandemic-related discontinuation or withdrawal up to Week 16 in part 2 only.
2. Section 8.3.1 Temporary Discontinuation of Study Drug		
Used to read: Subjects must be temporarily discontinued from study drug dosing in either event of: •Grade 3 neutrophil count (<1000-500/μL, per the National Institutes of Health/National Cancer Institute (NIH/NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (CTCAE v4.03, 2010).	Now reads: Subjects must be temporarily discontinued from study drug dosing in either event of: •Grade 3 neutrophil count (<1000-500/μL, per the National Institutes of Health/National Cancer Institute (NIH/NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (CTCAE v4.03, 2010).	Considering the current pandemic, an additional criterion of fever included in the list of events that may result in temporary discontinuation of study drug

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
•Grade 2 platelet count (<7.5 – 5.0 X 104/µL, per NIH/NCI-CTCAE).	•Grade 2 platelet count (<7.5 – 5.0 X 104/µL, per NIH/NCI-CTCAE). **•Fever (>100.4°F or >38°C), suspected infection, or infection requiring oral antibiotics.**	
3. Section 8.3.4 Enrollment of Additional Subjects		
Used to read: Section 8.3.4 Replacement of Subjects Not applicable.	Now reads: Section 8.3.4 ~~Replacement of Subjects~~ Enrollment of Additional Subjects ~~Not applicable.~~ **Special considerations have been added to the protocol based on the issues arising from the SARS-CoV-2/COVID-19 pandemic. During the blinded dosing period for Part 2 (ie, prior to completion of the Week 16 visit), any randomized subject who terminates study participation or who misses 2 or more consecutive doses of study drug (even if continuing with study participation) or misses any part of the primary endpoint assessments at Week 16, as a result of pandemic-related reasons, may not be counted against the total number of subjects targeted (N=156 for Part 2 of the study). For each of these cases, a new subject may be screened and randomized, to allow an evaluable number of subjects for the Week 16 primary endpoint. The new subjects in screening will receive new subject numbers and new treatment assignments as per the current randomization schedule in the protocol.** **Additional subjects will only be added in response to the number of subjects who meet the above criteria, as a result of pandemic-related issues. Randomized subjects who discontinue study participation or miss consecutive doses or the Week 16 primary endpoint assessments for non-pandemic related reasons, or who have study drug or study visit issues after completing their Week 16 visit, will**	Enrollment of additional subjects is now allowed due to pandemic-related discontinuation or withdrawal up to Week 16 in part 2 only.

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
	not trigger the screening of additional subjects.	
4. Section 9.4.1 Blinding and Unblinding Procedures		
Used to read: For the blinded treatment phase, in the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, or needs to be known to treat an individual subject for an AE, the medical monitor must be notified immediately by the Investigator and if possible, before unblinding. For the open-label treatment phase, drug preparation and administration should be handled by the same unblinded personnel as for the blinded treatment phase.	Now reads: For the blinded treatment phase, in the event that the treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, or needs to be known to treat an individual subject for an AE, the medical monitor must be notified immediately by the Investigator and if possible, before unblinding. For the open-label treatment phase, drug preparation and administration should be handled by the same unblinded personnel as for the blinded treatment phase. **In special circumstances (eg, during SARS-CoV-2/COVID-19 pandemic, which may prevent the subject from presenting to the site), the handling, preparation, and administration of the study drug (during blinded or open-label periods of the study) may be performed by an unblinded, qualified healthcare provider who is not involved in study management, such as a home-visit nurse contracted by the Sponsor (if such service is available at the time and where permitted by local regulations) (see Section 10.5).**	To include flexibility of dosing for the subject who may not come to the site in special circumstances
5. Section 10.4 Study Drug Preparation		
Used to read: Appropriate aseptic technique should be used while preparing and administering the injection. The designated, trained, unblinded pharmacist (or designee) will prepare and dispense study drug for each subject according to the subject's IWRS/IVRS assignment.	Now reads: Appropriate aseptic technique should be used while preparing and administering the injection. The designated, trained, unblinded pharmacist (or designee) will prepare and dispense study drug for each subject according to the subject's IWRS/IVRS assignment. **In special circumstances, (eg, during SARS-CoV-2/COVID-19 pandemic, which may prevent the subject from presenting to the site), an unblinded,**	To include flexibility of dosing for the subject who may not come to the site in special circumstances

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
	qualified healthcare provider may prepare study drug for injection (see Section 10.5).	
6. Section 10.5 Administration		
Used to read: The day of administration of the first dose of study drug (ISB 830 or placebo) is considered Day 1. Appropriate aseptic technique should be used while preparing and administering injections. Designated, trained, unblinded personnel (pharmacist or designee) will administer prepared study drug (see Section 10.4) to maintain the blind. The monitoring done following dosing will be conducted by blinded study personnel. The investigational product will be administered by SC injection by trained unblinded study staff.	Now reads: The day of administration of the first dose of study drug (ISB 830 or placebo) is considered Day 1. Appropriate aseptic technique should be used while preparing and administering injections. Designated, trained, unblinded personnel (pharmacist or designee) will administer prepared study drug (see Section 10.4) to maintain the blind. The monitoring ~~done~~ following dosing will be conducted by blinded study personnel. **In special circumstances, (eg, during SARS-CoV-2/COVID-19 pandemic, which may prevent the subject from presenting to the site), subjects may receive 'at home' dosing, performed by an unblinded, qualified healthcare provider (if such service is available at the time and where permitted by local regulations) who will perform vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [per minute] and oral or tympanic temperature [degrees in Celsius]) by standard methods prior to dosing, and who will conduct the protocol-specified observation post-injection. Women of childbearing potential will also be administered a monthly urine pregnancy test by the unblinded, qualified healthcare provider, and must have a negative pregnancy result prior to dosing.** **Additional details will be provided in the pharmacy manual and in a separate home healthcare provider manual.**	To include flexibility of dosing for the subject who may not come to the site in special circumstances

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
7. Synopsis, Section 13.1 Safety Parameters		
Used to read: Safety Assessments: Guidance will be given to the investigator for the criteria to be used to assess anaphylaxis (Sampson et al, 2006), see Section 13.2.1.4. Injection site reactions will be assessed according to the CTCAE v4.03 (CTCAE v4.03, 2010).	Now reads: Safety Assessments: Guidance will be given to the investigator for the criteria to be used to assess anaphylaxis (Sampson et al, 2006), see Section 13.2.1.4. Injection site reactions will be assessed according to the CTCAE v4.03 (CTCAE v4.03, 2010). **Pandemic Related Safety Assessments:** **To ensure the ongoing safety of subjects during the pandemic, study subjects who miss or are unable to attend scheduled clinic visits will be contacted by the site via a safety phone call that includes the collection of AEs/SAEs and concomitant medications. This phone call is to be performed for every missed visit that occurs during the pandemic. If the subject meets other criteria, eg, for withdrawal/discontinuation of the study drug, the site is to follow the protocol in regard to those criteria.** **Subject withdrawal/discontinuation criteria are outlined in Section 8.3.**	Additional safety measure included to ensure safety of subjects in the SARS-CoV-2/ COVID-19 pandemic
8. Synopsis, Section 15.1 Sample Size		
Used to read: [redacted]	Now reads: A sample size of 62 completed [redacted]	Enrollment of additional subjects is now allowed due to pandemic-related discontinuation or withdrawal up to Week 16 in part 2 only.

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
[redacted]	[redacted]	
9. Synopsis, Section 15.6 Efficacy Analyses		
Used to read: The primary efficacy analysis will be the percentage change from baseline in EASI score, and the secondary efficacy analysis will be the IGA and EASI 75 (subjects achieving 75% reduction from baseline in EASI score). The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The EASI and IGA scores will be assessed at time points described in the Schedule of Assessments. The primary efficacy analyses will be conducted for all subjects in the FAS using the treatment arm as assigned. For the primary and secondary endpoints, the efficacy analysis will be performed using the PPS. For both Part 1 and Part 2 of the study, the primary endpoint (percentage change from baseline in EASI score at Week 16) will be analyzed using a MMRM model. The model will adjust for study treatment, baseline, randomization stratification factors, baseline-by-treatment interaction and visit as the within-subject effect. The continuous secondary endpoints will be analyzed using the MMRM model as performed for the primary endpoint. The Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity)	Now reads: The primary efficacy analysis will be the percentage change from baseline in EASI score, and the secondary efficacy analysis will be the IGA and EASI 75 (subjects achieving 75% reduction from baseline in EASI score). The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The EASI and IGA scores will be assessed at time points described in the Schedule of Assessments. The primary efficacy analyses will be conducted for all subjects in the FAS using the treatment arm as assigned. ~~For the primary and secondary endpoints, the efficacy analysis will be performed using the PPS.~~ **In addition, the efficacy analyses for the primary endpoint and secondary endpoints (IGA, EASI-75) will be conducted using the PPS.** For both Part 1 and Part 2 of the study, the primary endpoint (percentage change from baseline in EASI score at Week 16) will be analyzed using a MMRM model. The model will adjust for study treatment, baseline, randomization stratification factors, ~~baseline-by-treatment interaction and visit as the within-subject effect~~ **visit as well as baseline-by-visit and treatment-by-visit interactions.** The continuous secondary endpoints will be analyzed using the MMRM model as performed for the primary endpoint.	To explain clearly the endpoints that will be conducted under the PPS. Updated to align with statistical analysis plan. Efficacy analyses for Part 2 was amended to include changes based on enrollment of additional subject due to pandemic-related issue

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
will be used to analyze the categorical secondary endpoints. To test the robustness of the MMRM model for the primary endpoint, sensitivity analyses using tipping point approach will be conducted. In addition, the primary endpoint will be analyzed using the complete dataset (subjects who complete the Week 16 and had EASI measurement). For Part 2 of the study, Group 5 ([redacted] loading dose/[redacted] mg q2w maintenance) will be compared to the corresponding placebo arm (Group 6) using the same statistical methods used in the analysis of the first part of the study.	The Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity) will be used to analyze the categorical secondary endpoints. To test the robustness of the MMRM model for the primary endpoint, sensitivity analyses using tipping point approach will be conducted. In addition, the primary endpoint will be analyzed using the complete dataset (subjects who complete the Week 16 and had EASI measurement). For Part 2 of the study, Group 5 ([redacted] loading dose/[redacted] q2w maintenance) will be compared to the corresponding placebo arm (Group 6) using the same statistical methods used in the analysis of the first part of the study. **To assess the robustness of the results in the Part 2 of the study, the analyses on primary endpoint and secondary endpoints (IGA, EASI-75) will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.**	

B. Details of Non-substantial Changes to the Protocol, from Version 9.0, Amendment 8 to Protocol Version 10.0, Amendment 9

From Protocol Version 9.0 (Amendment 8) 28-Jan-2020	To Protocol Version 10.0 (Amendment 9) 05-May-2020	Rationale for Amendment
1. Section 9.3 Treatment Compliance		
Used to read: Treatment compliance will be measured by the designated person administering the study drug (see Section 10.5) at the clinical study site.	Now reads: Treatment compliance will be measured by the designated person ~~administering the study drug~~ (see Section 10.5) at the clinical study site.	To include flexibility of dosing at home by an unblinded, qualified healthcare provider for the subject who may not come to the site in special circumstances

Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of GBR 830 in Adult Subjects With Moderate to Severe Atopic Dermatitis

Version 6.0; Dated: 21-September-2021

Protocol number: GBR 830-204

Sponsor: Ichnos Sciences SA

TITLE PAGE

STATISTICAL ANALYSIS PLAN
PHASE 2B

VERSION: 6.0

DATE OF PLAN
21-Sep-2021

BASED ON:
GBR 830-204 Protocol V10.0 05-May-2020

STUDY DRUG:
ISB 830

PROTOCOL NUMBER:
GBR 830-204

STUDY TITLE:
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF GBR 830 IN ADULT SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

SPONSOR:
Ichnos Sciences SA

This study is being conducted in accordance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

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TECHNICAL SUMMARY REPORT (TSR)

TSR is Synopsis section of the protocol.

Name of Sponsor/Company: Ichnos Sciences SA	
Name of Study Drug: ISB 830	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of GBR 830 in Adult Subjects with Moderate to Severe Atopic Dermatitis	
IND no: 126820	**EudraCT no:** 2018-000783-29
Phase of development: 2b	
Indication: Moderate to Severe Atopic Dermatitis	

Objectives:

Primary:

- To characterize the efficacy of ISB 830 monotherapy in adults with moderate-to-severe atopic dermatitis (AD) compared to placebo as measured by percentage change from baseline in Eczema Area and Severity Index (EASI) score at Week 16.

Secondary:

- To evaluate safety, tolerability, pharmacokinetics (PK), and immunogenicity of ISB 830 in adults with moderate-to-severe AD.
- To measure the effect of ISB 830 on disease activity in adult subjects with moderate-to-severe AD, as measured by validated tools (such as Investigator's Global Assessment [IGA], EASI response, SCORing Atopic Dermatitis [SCORAD]).

Exploratory:

- To evaluate pharmacodynamics (PD) of ISB 830 in adults with moderate-to-severe AD.

Study population:

Adult males and females (≥18 years of age) with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (eg, intolerance, other important side effects or safety risks in the opinion of the Investigator).

Moderate-to-severe AD is defined by an IGA score of 3 or higher at screening and baseline, consistent with the categories of moderate (IGA=3) and severe (IGA=4); and an EASI score of 12 or higher at screening or 16 or higher at baseline.

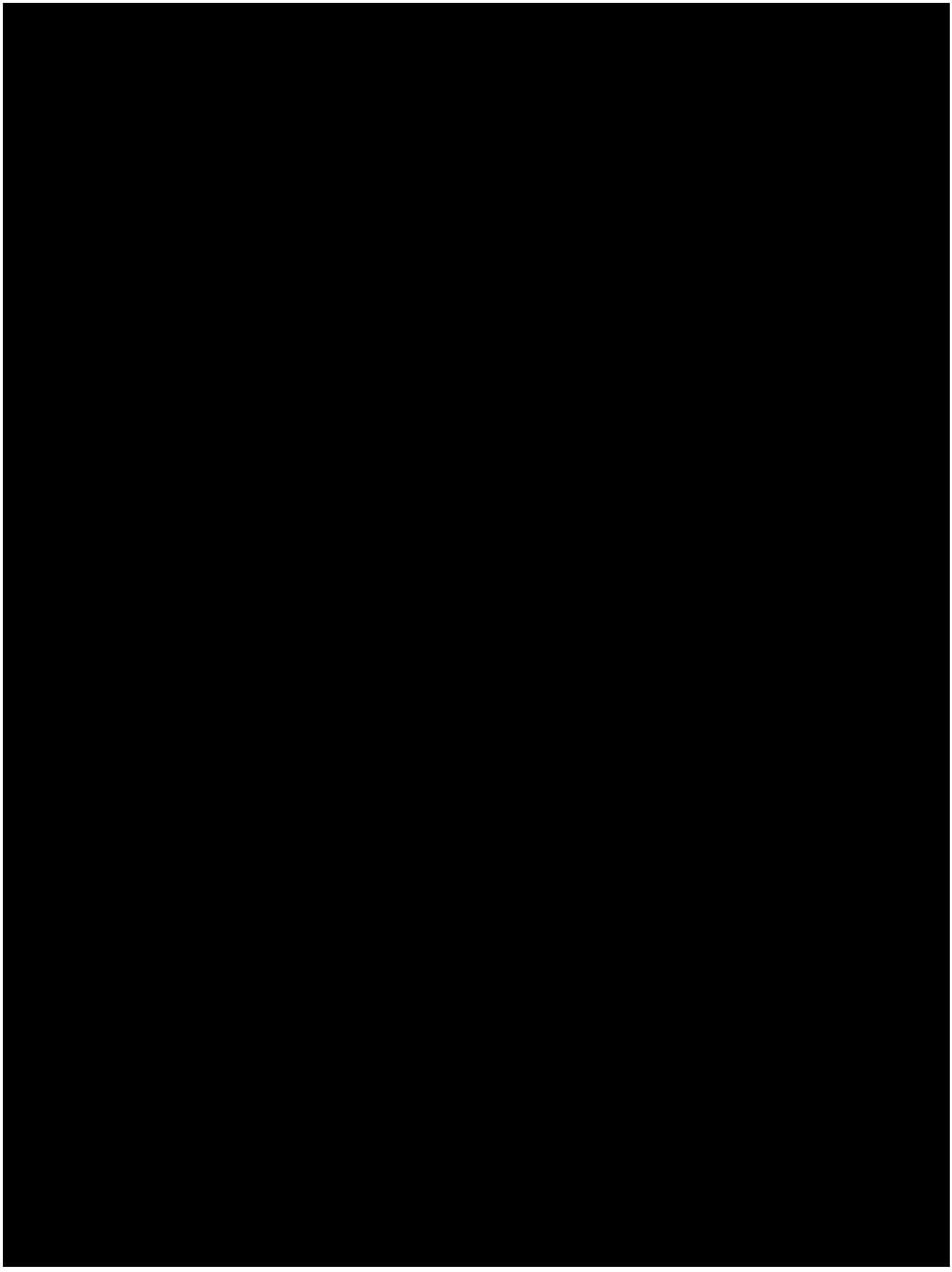
Study design:
This is a multicenter, double-blind, placebo-controlled study. The study will be conducted in 4 phases: a screening phase, a blinded treatment phase, an open-label treatment phase, and a follow-up phase. Subjects will participate in a 54-week treatment period (including 52 weeks of study drug administration) with 12 weeks follow-up at end of the treatment phase from Week 54 to Week 66. The study will be conducted in 2 Parts, with dosing Groups 1-4 comprising Part 1, and dosing Groups 5-6 comprising Part 2.
The blinded treatment phase consists of a randomized, placebo-controlled treatment with ISB 830 for 16 weeks at different dose levels (see below). The open-label treatment phase consists of a 38-week treatment phase where ISB 830 will be administered every other week (q2w) subcutaneously (SC). The primary endpoint of the study will be assessed at the end of the blinded treatment period at Week 16.
Subject eligibility will be assessed during screening, which will occur within 28 days prior to randomization. During the screening period, treatments for AD will be withdrawn or modified for the subject as defined in the protocol (Table 5). Subjects may be re-screened once (within or outside of the screening period) if they fail the screening evaluation. All screening procedures will be repeated during rescreening.
Subjects who continue to meet eligibility criteria will undergo Day 1/baseline (predose) assessments and will be randomized to equal groups of approximately 78 subjects each.
Subjects will receive SC injections of ISB 830, or corresponding placebo. A total of 27 doses (ISB 830 or placebo) will be administered q2w.
During the blinded treatment phase each subject will receive a dose on Day 1 and q2w starting from Day 15 through Week 14, according to the following treatment assignment and table below:
<u>Study Part 1:</u>

- Group 1: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume), starting at Day 15 (Week 2).
- Group 2: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by dosing every 4 weeks (q4w) of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of 2 mL) will be administered q4w starting at Day 15 (Week 2).
- Group 3: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q4w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted]) will be administered q4w starting at Day 15 (Week 2).
- Group 4: Dose of placebo (2 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (1 SC injection of [redacted]) starting at Day 15 (Week 2).

<u>Study Part 2:</u>

- Group 5: [redacted] ISB 830 (4 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (2 SC injections containing [redacted] volume), starting at Day 15 (Week 2).
- Group 6: Dose of placebo (4 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (2 SC injections of [redacted]) starting at Day 15 (Week 2).

During the blinded treatment phase all subjects in Groups 1 through 4 will receive a loading dose consisting of 2 SC injections, followed by 7 maintenance doses consisting of 1 SC injection per dose. For Groups 5 and 6, all subjects will receive a loading dose consisting of 4 SC injections, followed by 7 maintenance doses consisting of 2 SC injections per dose, as described above and in protocol Section 10.1, Table 6.
During the open-label treatment phase each subject will receive 19 doses of ISB 830 SC injection [redacted]) q2w (consisting of 1 to 2 SC injections per dose, respectively) from Week 16 to Week 52 or until subject withdrawal, as described above and in protocol Section 10.1, Table 6.
All subjects in Groups 1-4 in the open-label treatment phase will receive [redacted] q2w. All subjects in Groups 5-6 in the open-label treatment phase will receive [redacted] q2w.



Safety assessments, clinical laboratory assessments, vital sign assessments, PK sampling, immunogenicity sampling, and clinical efficacy assessments (IGA and EASI) will be performed by the blinded Investigator and blinded study staff as defined in Table 2 of the protocol (Schedule of Assessments), or until the subject discontinues from the study.

An experimental population PK design will be used for the PK blood sampling. The subjects in the rich PK group will have additional blood sampling between Days 1 to 8 (Week 1), and Days 85 to 92 (Week 12) compared to the sparse PK group. The subjects in the sparse PK group will have widespread sampling with fewer time points for each subject (compared to the rich PK group). Approximately 80 rich PK subjects will be randomized (in a 1:1:1:1 ratio) to treatment groups 1-4 and approximately 40 rich PK subjects will be randomized (in a 1:1 ratio) to treatment groups 5 and 6. The remaining subjects in the study will be included in the sparse PK group. Blood samples will be collected from the rich and sparse PK subjects according to the respective schedule described in Table 8 of the protocol.

End-of-treatment (EOT) visits will be conducted on Day 113 (Week 16) for the blinded treatment phase and at Day 379 (Week 54) for the open-label treatment phase for all subjects. Subjects should continue into the follow-up period and will have a follow-up phone call 4 and 8 weeks after the last EOT visit [Day 407 (Week 58) and Day 435 (Week 62) respectively] and a final clinic visit 12 weeks after the EOT [Day 463 (Week 66)] visit.

Subjects who withdraw consent from the blinded treatment phase prior to Week 16 will undergo the blinded treatment phase EOT visit procedures and enter the follow-up period.

Subjects who withdraw consent from open-label treatment phase prior to Week 52 will undergo the open-label treatment phase EOT visit procedures and enter the follow-up period.

All subjects continuing in the follow-up period will have a follow-up phone call 4 and 8 weeks after the last EOT visit and a final clinic visit 12 weeks after the EOT visit as described in the Table 3 follow-up period.

Subjects will be clinically monitored for safety throughout the study, including anaphylactic reactions and/or injection site reactions (ISRs), with monitoring at the study site for 2 hours after the first dose on Day 1 (in the blinded treatment phase) and on Day 113 (Week 16) (first dose in open-label treatment phase) and for 1 hour after dosing at all other visits.

To allow subjects access to the open-label treatment phase of the study, subjects who have completed the GBR 830-204 study prior to implementation of the protocol amendment that includes the open-label phase (eg, Protocol Amendment 3 (version 4.0) and/or Amendment 6 (version 7.0)) or who are in the follow-up phase of the study at the time of implementation of the open-label protocol amendment, may be eligible to participate in the open-label treatment phase of this study. Subjects who have completed the study prior to implementation of the open-label protocol amendment must undergo a modified Screening visit (as per Table 2 of the protocol), and if eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1and 5), will undergo study assessments as per Table 3 of the protocol. Subjects who are in the follow-up period of GBR 830-204 at the time the open-label protocol amendment is implemented must complete their follow-up period as per protocol, and then must undergo a modified Screening visit (as per Table 2 of the protocol), and if eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1 and 5), will undergo study assessments as per Table 3 of the protocol. This includes a complete washout of any concomitant medications and therapies received (as per Table 5 of the protocol) prior to starting the open-label treatment phase of the study.

Study endpoints:

Primary Endpoint:

- Percentage change from baseline in EASI score at Week 16.

Secondary Endpoints:

Efficacy Endpoints:

- Proportion of subjects with EASI-75 (≥75% improvement from baseline) at Week 16.
- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points at Week 16.

- Proportion of subjects with improvement (reduction) of Pruritus Numerical Rating Scale (NRS) ≥4 from baseline to Week 16.
- Proportion of subjects who achieve an EASI 50 (≥50% improvement from baseline) response from baseline through Week 16.
- Change in SCORAD from baseline through Week 16.
- Change in the Dermatology Life Quality Index (DLQI) from baseline through Week 16.
- Change in Global Individual Signs Score (GISS) (erythema, infiltration/papulation, excoriations, lichenification) from baseline through Week 16.
- Change in Hospital Anxiety Depression Scale (HADS) from baseline through Week 16.
- Change in Patient Oriented Eczema Measure (POEM) from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Disease from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Treatment from baseline through Week 16.
- Assessment of sick leave and/or missed school days through Week 16.

Safety Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through Week 16 and Week 54.
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of conjunctivitis TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through Week 16 and Week 54.
- Incidence of TEAEs leading to treatment discontinuation from baseline through Week 16 and Week 54.
- Overall number of TEAEs and SAEs through Week 16 and Week 54.
- Vital signs, clinical laboratory values, and electrocardiogram (ECG) results monitored from baseline through Week 16 and Week 54.
- Formation of anti-drug antibodies (ADA) to ISB 830 to evaluate immunogenicity.

Pharmacokinetics Endpoints:

- C_{max}, t_{max}, AUC_{tau}, AUC_{0-t}, and other related parameters will be estimated using data from the rich PK group from the blinded treatment phase. C_{trough} values will be estimated using data from both rich and sparse PK groups from the blinded treatment phase.

Exploratory Endpoints:

Samples for exploratory biomarker endpoints will be collected when and where biomarker sample kits are available.

Exploratory biomarker endpoints are:

- Messenger RNA (mRNA) expression of immune and barrier measures in skin biopsies at baseline, end of Week 8, and end of Week 16.
- Biomarker analysis in ISB 830 responder and non-responder populations to evaluate the relationship of biomarkers with clinical efficacy measures.
- Assays on plasma, serum, viably frozen peripheral blood mononuclear cells (vfPBMCs) and/or cell subsets/derivatives.

Exploratory efficacy endpoints are:

- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points through Week 54.
- Proportion of subjects with EASI-75 (≥75% improvement from baseline) through Week 54.
- Proportion of subjects who achieve an EASI-50 (≥50% improvement from baseline) through Week 54.
- Change in the European Quality of Life Status (EQ-5D) through Week 16.
- Change in Juniper Asthma Control Questionnaire (ACQ-5) from baseline through Week 16.
- Change in the Sino-nasal Outcome Test (SNOT-22) from baseline through Week 16.
- To assess qualitative changes in photographs of skin lesions taken at time points specified in the Schedule of Assessment.

Number of subjects (planned):

For Groups 1 through 4, a sufficient number of subjects will be screened to randomize approximately 312 eligible subjects in a 1:1:1:1 ratio. For Groups 5 and 6, a sufficient number of subjects will be screened to randomize approximately 156 eligible subjects in a 1:1 ratio to either ISB 830 or placebo, therefore approximately 468 subjects are planned to be randomized in this study. The randomization will be stratified by disease severity (moderate or severe, as assessed by IGA), geographic region (North America vs European Union), and subjects consenting to rich PK sampling (Yes/No). The actual number of subjects randomized in Groups 5 and 6 may be different than initially planned due to the impact of the SARS-CoV-2/COVID-19 pandemic (see protocol Section 8.3.4).

Main criteria for inclusion:

1. Provided written informed consent and any locally required authorization prior to any protocol-related procedures, including screening evaluations.
2. Willing and able to comply with all aspects of the protocol.
3. Male or female ≥18 years at the time of screening.
4. Physician diagnosis of AD for > 1 year; diagnosis of AD as defined by the American Academy of Dermatology Consensus Criteria (Eichenfield et al, 2014).
5. AD involvement of ≥10% Body surface area (BSA) at screening and baseline.
6. EASI score of ≥12 at screening or ≥16 at baseline.
7. IGA score of ≥3 at screening and baseline (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe).
8. Baseline Pruritus NRS score for maximum itch intensity ≥3 over the previous 24 hours. A minimum of 3 days of diary completion is required in the week prior to randomization.
9. Documented/reported recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications (topical corticosteroids or crisaborole or topical calcineurin inhibitors) or subjects for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks as defined in the protocol). Documents may include medical

records, physician to healthcare provider communication (with date and time of communication and physician signature), or, pharmacy records (with clearly listed dates of dispensation). A course of marketed systemic immunosuppressants (eg, prednisone, cyclosporine, and methotrexate) for AD in the 6 months prior to screening assumes failure of topicals and is acceptable in place of topical failure.

10. Have applied a stable dose of topical emollient (moisturizer) twice-daily for at least 7 consecutive days immediately before the baseline visit (with the exception of prohibited moisturizers containing additives listed in Exclusion Criteria #5).
11. Must agree to the following requirements during the study:
    a. If female and of childbearing potential, she must have a negative serum pregnancy test result within 7 days prior to first dosing and a negative urine pregnancy test predose on Day 1. She must be willing to use a highly effective form of contraception (ICH E8 Guideline, 1997; (ICH M3 [R2] Guidance, 2009; (FDA M3 [R2] Guidance, 2010) for the duration of the study and for at least 3 months after the last dose of study medication. Methods like periodic abstinence, post ovulation procedures and withdrawal are not considered adequate. Each woman will be considered to have childbearing potential unless she has been surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy or has been post-menopausal for at least 2 years. For postmenopausal women only, follicle stimulating hormone (FSH) testing will be performed at screening to confirm non-childbearing potential (FSH ≥40 IU/L).
    b. If male with a partner of childbearing potential, he must be willing to use condoms in combination with a second effective method of contraception during the study. Each man will be considered as potent unless surgically sterilized (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate). Male subjects must continue to use contraception for 180 days following administration of the study drug.
    c. Male subjects should agree not to donate sperm during the study and for 180 days following administration of the study drug.

Main criteria for exclusion:

1. Prior treatment with ISB 830.
2. Employee of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
3. Concurrent enrollment in another investigational clinical study.
4. Treatment with any of the following before baseline:
    a. Investigational biological agent within 8 weeks of baseline or 5 half-lives, whichever is longer.
    b. Investigational drugs eg, phosphodiesterase type 4 (PDE4) inhibitors, Janus kinase (JAK) inhibitors, within 4 weeks of baseline.
    c. Phototherapy for AD within 4 weeks of baseline.
    d. Marketed drugs, including systemic corticosteroids, immunosuppressive/immunomodulatory drugs including but not limited to cyclosporine, mycophenolate mofetil, interferon-gamma (IFN-γ), PDE4 inhibitors, JAK inhibitors, azathioprine or methotrexate within 4 weeks of baseline.
    e. Topical medications, including corticosteroids, tacrolimus, and/or pimecrolimus, and crisaborole within 1 week of baseline.
    f. Regular use (>2 visits/week) of a tanning booth/parlor within 4 weeks of baseline.
    g. Biologics, depending on the type of biologic such as cell-depleting agents including but not limited to rituximab: within 6 months of baseline, or until lymphocyte and CD19+ lymphocyte count returns to normal, whichever is longer.
    h. Biologics including infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, etanercept, anakinra, dupilumab: within 12 weeks of baseline, or 5 half-lives, whichever is longer.
    i. Other biologics: within 5 half-lives (if known).
5. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (subjects may continue using stable doses of such moisturizers if initiated before the screening visit).
6. Planned or anticipated use of any prohibited medications and procedures during study treatment as defined in the study protocol.

7. Subjects who are immunocompromised (congenital or acquired), or who have had a recent (within 3 months prior to baseline) or current serious systemic infection (including infectious mononucleosis-like illness or herpes zoster).
8. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit.
9. Subjects who have evidence of active or latent tuberculosis (TB) as documented in their medical history or test positive at screening. For indeterminate cases, an informed decision will be made between the Principal Investigator and Medical Monitor.
10. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: subjects may be rescreened after infection resolves.
11. Presence of skin comorbidities that may interfere with study assessments, in the opinion of the Investigator, including subjects with psoriasis.
12. Poorly controlled asthma as assessed by the Asthma Control Questionnaire [ACQ] based on International ERS/ATS guidelines.
13. Any condition at baseline which is part of the criteria for discontinuation of study drug as defined in the study protocol.
14. Subjects who are known to be seropositive for human immunodeficiency virus (HIV) or who test positive at screening.
15. History of a positive result for Hepatitis B surface antigen (HBsAg), antibody to Hepatitis B core antigen (anti-HBcAg), or antibody to Hepatitis C virus (anti-HCV) or presence of these findings at screening.
16. History of alcohol or drug abuse within 2 years of the screening visit.
17. Subjects with a history of non-malignant lymphoproliferative disorders, or a history of malignancy within 5 years before baseline (except completely treated in situ cervical carcinoma or non-metastatic squamous or basal cell carcinoma of the skin).
18. In the opinion of the Investigator, subjects with any other medical or psychological condition as well as laboratory values, which are significantly different from normal reference ranges and/or judged to be clinically significant; and/or any condition that would interfere with evaluation of the study drug or interpretation of subject safety or study results, including conditions that are inadequately understood at the time of screening.
19. Subjects with a history of substance abuse or dependence that in the opinion of the Investigator, is considered to interfere with the subject's participation in the study.
20. Planned or anticipated major surgical procedure during the subject's participation in this study.
21. Women who are pregnant or breast feeding.
22. Known hypersensitivity to monoclonal antibodies or any of the excipients of the drug product.

Estimated Duration of subject participation:
The anticipated maximum total study duration for each subject is approximately 70 weeks. This duration will consist of the screening period of up to 4 weeks, the blinded treatment period of up to 16 weeks (14 weeks of treatment, with a loading dose on Day 1 followed by maintenance dosing from Day 15 [Week 2] until the last dose at Week 14), the open-label treatment period of up to 38 weeks, and the follow-up period of 12 weeks starting at the end of the open-label treatment period. Subjects who consent to participate in the open-label treatment phase of the study after they completed the GBR 830-204 study, and require a modified screening visit, would have a study participation duration of up to 86 weeks.

Duration of treatment:
There is a 54-week treatment period (consisting of 52 weeks of dosing, including a blinded loading dose on Day 1 followed by blinded maintenance dose from Week 2 until Week 14, followed by open-label treatment dose from Week 16 to Week 52).

Investigational product, dosage and mode of administration:
Name of Investigational Product: ISB 830

Dosage Form: [redacted]

Dosage for blinded treatment phase: See Groups 1, 2, 3, and 5 in the Treatment Groups and Dose Regimens table, in the Study Design section above.
Dosage for open-label treatment phase: All subjects in Groups 1-4 in the open-label treatment phase will receive [redacted] of ISB 830 q2w. All subjects in Groups 5-6 in the open-label treatment phase will receive [redacted] q2w.
Mode of Administration: SC injection

Placebo therapy, dosage and mode of administration:
Placebo/Control: Placebo for ISB 830
Dosage Form: [redacted]

Dosage for blinded treatment phase: See Groups 2, 3, 4 and 6 in the Treatment Groups and Dose Regimens table, in the Study Design section above.
Dosage for open-label treatment phase: Not applicable.
Mode of Administration: SC injection

Criteria for evaluation:
Efficacy Assessments:

- The EASI is a validated measure used in clinical practice and clinical studies to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head/neck, trunk (including genital area), upper limbs, and lower limbs (including buttocks), and converted to a score of 0 to 6 (Hanifin et al, 2001).
- The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe).
- The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and intensity of AD. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The intensity of 6 specific symptoms of AD is assessed using the following scale: absence (0), mild (1), moderate (2), or severe (3), (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of pruritus and sleep-loss is recorded for each symptom by the subject or relative on a visual analogue scale (VAS), where 0 is no pruritus (or sleep-loss) and 10 is the worst imaginable pruritus (or sleep-loss), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: $A/5 + 7B/2 + C$ (Kunz et al, 1997).
- Pruritus Numerical Rating Scale (NRS): Subjects will respond to the following question, "On a scale of 0 – 10, with 0 being no itch and 10 being the worst itch imaginable, how would you rate your worst degree of itch during the previous 24 hours?" The Pruritus NRS will be assessed by the subject once per day in the morning, ideally at the same time; recorded by the subject after each assessment, and reviewed by study staff at each clinic visit.
- DLQI: The DLQI is a subject-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work, and school and personal relationships and treatment. Response categories include "a little," "a lot," and "very much" with corresponding scores of 1, 2, and 3, respectively; "not at all," "not relevant" responses are scored as "0." Totals range from 0 to 30 (ie, from less to more impairment), and a 5 point change from baseline is considered clinically relevant (Finlay and Khan, 1994; Basra et al, 2008).

- GISS: Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria.
- Body Surface Area Involvement of Atopic Dermatitis (BSA): Body surface area affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.
- HADS: The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond and Snaith, 1983; Hermann, 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.
- POEM: The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman et al, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.
- EQ-5D: The EQ-5D is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3).
- ACQ-5: The ACQ-5 is a 5-question version of the Juniper ACQ and is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of subjects with a medical history of asthma.
- SNOT-22: The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life. The questionnaire will be administered only to a subset of subjects (eg, with chronic rhinitis/ rhinosinusitis, nasal polyps, allergic rhinitis).
- Patient Global Assessment of Disease: Subjects will rate their overall well-being based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent."
- Patient Global Assessment of Treatment: Subjects will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "How would you rate the way your eczema responded to the study medication?" Response choices are: "Poor"; "Fair"; "Good"; "Very Good"; "Excellent."
- Assessment of Sick Leave and/or Missed School Days: Subjects who are employed or enrolled in school will be asked to report the number of sick leave and/or missed school days due to atopic dermatitis (eg, vs due to an accident) in the last 4 weeks.

Pharmacokinetic Assessments:
Blood samples will be collected from both rich and sparse PK groups at appropriate time points defined in Tables 2 and 3, and Table 8 in the protocol.
The serum concentrations of ISB 830 in these samples will be quantified using a validated enzyme-linked immunosorbent assay (ELISA) method. Serum concentration data from both rich PK and sparse PK group from the blinded treatment phase will be used to derive PK parameters, as appropriate.
Immunogenicity Assessments:
Blood samples will be collected at appropriate time points defined in Tables 2 and 3, and Table 8 in the protocol to detect the presence of anti-drug antibodies (ADA) to ISB 830, as per procedures similar to collection of PK

samples. The presence or absence of ADA in these samples will be determined using a validated Electrochemiluminescence immunoassay (ECLIA) method.

Pharmacodynamic (Biomarker) Assessments:

Blood samples, including plasma, serum, whole blood, viably frozen peripheral blood mononuclear cells (vfPBMCs) and/or cell subsets will be collected from subjects randomized in the study at appropriate time points as defined in Table 2 and Table 8 in the protocol. Biomarker assessments to be performed on collected samples may include but not limited to:

- Leukocyte sub-population cell counts by flow cytometry
- Cytokines
- Biomarker in peripheral blood
- Total immunoglobulin E (IgE)
- Serum soluble OX40 ligand (OX40L) and serum soluble OX40
- Epigenetics

Exploratory Photographs:

Subjects, who agree to participate in the main study, also agree to allow photography of their skin (excluding pictures of the subject's face) during study participation at specified time points as per Table 2 and Table 3. Photographs of the subject's skin (with the exception of the face) may also be taken at additional time points, as per investigator judgment.

The photographs may be used to examine disease activity, autoimmunity/inflammation, ISB 830 mechanism of action, and/or the effect of the study drug(s) on the course of disease.

Details of photograph collection, processing, shipping and storage will be provided to the study sites in a separate manual.

Optional Genetic Research/Pharmacogenomics Assessments:

Subjects who provide written consent for Optional Genetic Research agree to provide a blood sample (one sample may be collected at any visit during the study) to evaluate genetic sequences that may be involved in disease activity, inflammation, study drug mechanism of action, PK/metabolism, and/or the effect of the study drug(s) on the course of disease. Subjects may decline this optional research without effect on their participation in the main study.

Safety Assessments:

Safety and tolerability of ISB 830 will be assessed based on adverse events (AEs), including anaphylactic events and ISRs; SAEs; vital signs; physical examinations; ECGs; and clinical laboratory parameters.

Subjects will be clinically monitored for safety throughout the study, including anaphylactic reactions and/or ISRs, with special monitoring at the study site for 2 hours after the first dose on Day 1 (in the blinded treatment phase) and on Day 113 (Week 16) (first dose in open-label treatment phase) and for 1 hour after dosing at all other visits.

Guidance will be given to the investigator for the criteria to be used to assess anaphylaxis (Sampson et al, 2006).

Injection site reactions will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 that was published 14-Jun-2010 by the US Department of Health and Human Services (National Institutes of Health [NIH] and National Cancer Institute [NCI]).

Pandemic Related Safety Assessments:

To ensure the ongoing safety of subjects during the pandemic, study subjects who miss or are unable to attend scheduled clinic visits will be contacted by the site via a safety phone call that includes the collection of AEs/SAEs and concomitant medications. This phone call is to be performed for every missed visit that occurs during the pandemic. If the subject meets other criteria, eg, for withdrawal/discontinuation of the study drug, the site is to follow the protocol in regard to those criteria.

STATISTICAL METHODS:

For both Part 1 and Part 2 of the study, the primary endpoint will be analyzed using a mixed-effect model for repeated measures (MMRM). The model will adjust for study treatment, baseline, randomization stratification factors, visit as well as baseline-by-visit and treatment-by-visit interactions.

The continuous secondary endpoints will be analyzed using the MMRM model as performed for the primary endpoint.

The Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity) will be used to analyze the categorical secondary endpoints.

For Part 2 of the study, Group 5 ([redacted] loading dose/[redacted] q2w maintenance) will be compared to the corresponding placebo arm (Group 6) using the same statistical method used in the analysis of the first part of the study.

To assess the robustness of the results in the Part 2 of the study, the analyses on primary endpoint and secondary endpoints (IGA, EASI-75) will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

Parts 1 and 2 are two independent parts of the study protocol and will therefore be analyzed separately. That is, upon completion of the double-blind period of Part 1, the database will be partially locked. The data will be analyzed and the topline results (TLR) determined. Similar activities will take place upon the completion of the double-blind period of Part 2.

The efficacy results from these 2 parts of the study will be kept separate. However, the safety results will be presented side by side.

Details of efficacy, safety and PK analyses will be specified in the Statistical Analysis Plan (SAP) and included in the Clinical Study Report (CSR). Population pharmacokinetic and exposure-response modeling will be described in a Modeling Plan and data will be published in a separate report.

Biomarker analyses will not be part of the CSR and will be described separately.

Study Populations:

Full Analysis Set:

The Full Analysis Set (FAS) consists of all subjects who are randomized and received at least 1 dose of study medication. Based on the intent-to-treat principle, subjects will be analyzed according to the treatment group assigned.

Per Protocol Set:

The Per Protocol Set (PPS) consists of all FAS subjects who have no major protocol deviations of eligibility or on-treatment study conduct.

Safety Analysis Set:

The Safety Analysis Set (SAS) consists of all subjects who were randomized and took at least 1 dose of study medication. Subjects will be analyzed according to the treatment they received.

Pharmacokinetic Analysis Set:

The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAS population who received ISB 830 and for whom sufficient serum concentration data are available to facilitate derivation of PK parameters, do not have any major protocol deviation, and for whom the time of dosing and the time of sampling are known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time points from the PKAS will be documented in the SAP.

Determination of Sample Size:

[redacted]

Efficacy Analyses:
The primary efficacy analysis will be the percentage change from baseline in EASI score, and the secondary efficacy analysis will be the IGA and EASI 75 (subjects achieving 75% reduction from baseline in EASI score). The IGA is an assessment instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The EASI and IGA scores will be assessed at time points described in the Schedule of Assessments.
To test the robustness of the MMRM for the primary endpoint, sensitivity analyses using the tipping point approach will be conducted. In addition, the primary endpoint will be analyzed using the complete dataset (subjects who complete the week 16 and had EASI measurements).
Detailed statistical methods, , the handling of missing data for the analysis of the primary as well as secondary and exploratory endpoints and the exploratory analyses on biomarkers will be described in the SAP and the Biomarker Analyses Plan.

Pharmacokinetic Analyses:
The PKAS will be used for the PK analyses. Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, and other related parameters) will be estimated using data from the rich PK group from the blinded treatment phase. Estimates of C_{trough} will be derived using the data from both rich PK group and sparse PK group from the blinded treatment phase. The PK parameters will be summarized in tabular and graphic form. Details of the PK analysis will be specified in the SAP.
The serum concentration data from both rich and sparse PK group may be used for the population PK analysis and will be reported separately.

Immunogenicity Analyses:
The number and percent incidence of positive and negative ADA status of subjects by treatment, and time points will be provided. Titers and neutralizing potential of confirmed positive samples will be reported. Details will be provided in the SAP.

Pharmacodynamic (Biomarker) Analyses:
Summary statistics will be provided for PD biomarkers.
Biomarker analyses will not be part of the CSR and will be described separately.

Safety Analyses:
Adverse events will be summarized by system organ class and preferred term. Subjects will be counted only once for each preferred term, system organ class, and by the highest severity of an event. Laboratory evaluations will be summarized with descriptive statistics at each visit, and change from baseline summarized for each post-baseline visit. Laboratory measurements will also be summarized based on the number and percentage of subjects above or below a pre-specified threshold for each test. AEs will be coded using MedDRA. Details will be presented in the GBR 830-204 SAP.

Data Safety Monitoring Board:
This study will institute a data safety monitoring board (DSMB) which will function independently of all other individuals associated with the conduct of this clinical study, including the site investigators participating in the study. The DSMB will be constituted prior to the randomization of the first subject. The DSMB will monitor subject safety by formally reviewing accumulated safety data by treatment group three times during the study. This includes but does not limit the role of the DSMB to evaluate these data and to provide recommendations to the sponsor to continue or modify the follow-up phase of the study as outlined in the DSMB charter.
It is expected that the DSMB will consist at a minimum of 2 physicians with appropriate disease area qualifications and 1 statistician. There will be a meeting with the DSMB describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DSMB charter.

Interim analyses:
No interim analyses are planned.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: List of Abbreviations

Abbreviation	Term or Definition
ACQ-5	Asthma Control Questionnaire-5
AD	Atopic Dermatitis
ADA	Anti-drug antibody (ies)
ADaM	Analysis Dataset Model
ADL	Activities of daily living
AE	Adverse Event
AIC	Akaike's Information Criterion
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from time 0 to infinity
AUC_{0-t}	Area under the curve from time 0 to the last measurable concentration
AUC_{0-tau}	Area under the curve over dosing interval
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BSA	Body Surface Area
C_{max}	Maximum observed plasma concentration
C_{trough}	Serum concentrations at end of dosing interval
CDISC	Clinical Data Interchange Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence immunoassay
eCRF	Electronic Case Report Forms

Abbreviation	Term or Definition
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	End-of-treatment
EOS	End of Study
EQ-5D	EuroQoL 5-Dimension
EU	European Union
FAS	Full Analysis Set
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HBcAg	Hepatitis B core Antigen
HBsAg	Hepatitis B surface Antigen
HEENT	Heads, eyes, ears, nose and throat
HIV	Human Immunodeficiency Virus
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IM	Immunogenicity
IRB	Institutional Review Board
IS	Immunogenicity
ISR	Injection Site Reaction
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LLOQ	Lower Limit Of Quantitation
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-effect Model for Repeated Measures
MNAR	Missing Not At Random
NAm	North America
NCI	National Cancer Institute

Abbreviation	Term or Definition
NIH	National Institutes of Health
NRS	Numeric Rating Scale
PD	Pharmacodynamic(s)
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PKAS	Pharmacokinetics Analysis Set
POEM	Patient-Oriented Eczema Measure
PPS	Per-Protocol Set
PT	Preferred Term
q2w	Every two weeks
q4w	Every four weeks
QCD	Quantitative Clinical Development
QoL	Quality of Life
QTc	Corrected QT
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous(ly)
SCORAD	SCORing Atopic Dermatitis
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SNOT	Sino-nasal Outcome Test
SOC	System Organ Class
TCI	Topical Calcineurin Inhibitor
TCS	Topical Corticosteroid
TEAE	Treatment-Emergent Adverse Event
TLFs	Tables, Listings and Figures
TLR	Topline Results
TSR	Technical Summary Report
UN	Unstructured
VAS	Visual Analogue Scale

Abbreviation	Term or Definition
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP is based on study protocol GBR 830-204 Version 10.0, Amendment 9. It describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

Details of efficacy, safety and pharmacokinetic (PK) analyses will be specified in this SAP and included in the Clinical Study Report (CSR). Detailed statistical methods, including methods for the handling of missing data for analyzing the primary, secondary and exploratory endpoints will be described in this SAP. This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database Lock (unblinding) of the study data. The reader of this SAP should also read the clinical protocol, and other relevant documents for details on the planned conduct of this study. Operational aspects including the protocol Schedule of Assessments (Table 2 and Table 3 in the protocol) related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

Population pharmacokinetic and exposure-response modeling will be described in a Modeling Plan and data will be published in a separate report. Biomarker analyses will not be part of the CSR and will be described separately.

3. STUDY OBJECTIVES AND PURPOSE

3.1. Study Objectives

3.1.1. Primary Objective

- To characterize the efficacy of ISB 830 monotherapy in adults with moderate-to-severe atopic dermatitis (AD) compared to placebo as measured by percentage change from baseline in Eczema Area and Severity Index (EASI) score at Week 16.

3.1.2. Secondary Objectives

- To evaluate safety, tolerability, PK and immunogenicity of ISB 830 in adults with moderate-to-severe AD.
- To measure the effect of ISB 830 on disease activity in adult subjects with moderate-to-severe AD, as measured by validated tools (such as Investigator's Global Assessment (IGA), EASI response, SCORing Atopic Dermatitis (SCORAD)).

3.1.3. Exploratory Objectives

- To evaluate pharmacodynamics (PD) of ISB 830 in adults with moderate-to-severe AD.

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Percent change from baseline in EASI score at Week 16.

3.2.2. Secondary Endpoints

Efficacy endpoints are:

- Proportion of subjects with EASI-75 (≥75% improvement from baseline) at Week 16 (key secondary endpoint).
- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) plus an IGA reduction from baseline of ≥2 points at Week 16 (key secondary endpoint).
- Proportion of subjects with improvement (reduction) of Pruritus Numerical Rating Scale (NRS) ≥4 from baseline to Week 16.
- Proportion of subjects who achieve an EASI-50 (≥50% improvement from baseline) response from baseline through Week 16.
- Change in SCORAD from baseline through Week 16.
- Change in the Dermatology Life Quality Index (DLQI) from baseline through Week 16.
- Change in Global Individual Signs Score (GISS) (erythema, infiltration/papulation, excoriations, lichenification) from baseline through Week 16.
- Change in Hospital Anxiety Depression Scale (HADS) from baseline through Week 16.
- Change in Patient Oriented Eczema Measure (POEM) from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Disease from baseline through Week 16.
- Absolute and percent change in Patient Global Assessment of Treatment from baseline through Week 16.
- Assessment of sick leave and/or missed school days through Week 16.

Safety endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs) from baseline through Week 16 and Week 54.
- Incidence of skin infection TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of conjunctivitis TEAEs requiring systemic treatment from baseline through Week 16 and Week 54.
- Incidence of treatment-emergent serious adverse events (SAEs) from baseline through Week 16 and Week 54.
- Incidence of TEAEs leading to treatment discontinuation from baseline through Week 16 and Week 54.

- Overall number of TEAEs and SAEs through Week 16 and Week 54.
- Vital signs, clinical laboratory values, and electrocardiogram (ECG) results monitored from baseline through Week 16 and Week 54.
- Formation of anti-drug antibodies (ADA) to ISB 830 to evaluate immunogenicity.

Pharmacokinetics endpoints are:

- C_{max}, t_{max}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, and other related parameters will be estimated using data from the rich PK group from the blinded treatment phase. Ctrough values will be estimated using data from both rich and sparse PK groups from the blinded treatment phase.

3.2.3. Exploratory Endpoints

Exploratory efficacy endpoints are:

- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points through Week 54.
- Proportion of subjects with EASI-75 (≥75% improvement from baseline) through Week 54.
- Proportion of subjects who achieve an EASI-50 (≥50% improvement from baseline) through Week 54.
- Change in the European Quality of Life Status (EQ-5D) through Week 16.
- Change in Juniper Asthma Control Questionnaire (ACQ-5) from baseline through Week 16.
- Change in the Sino-nasal Outcome Test (SNOT-22) from baseline through Week 16.
- To assess qualitative changes in photographs of skin lesions taken at time points specified in the Schedule of Assessment (Table 2 and Table 3 in the protocol).

4. OVERALL STUDY DESIGN

4.1. Summary of Study Design

This is a multicenter, double-blind, placebo-controlled study. The study will be conducted in 4 phases: a screening phase, a blinded treatment phase, an open-label treatment phase, and a follow-up phase. Subjects will participate in a 54-week treatment period (including 52 weeks of study drug administration) with 12 weeks follow-up from the end-of-treatment (EOT) visit (Week 54 to Week 66). The study will be conducted in 2 Parts, with dosing Groups 1-4 comprising Part 1, and dosing Groups 5-6 comprising Part 2.

The blinded treatment phase consists of a randomized, placebo-controlled treatment with ISB 830 for 16 weeks at different dose levels (see below). The open-label treatment phase consists of a 38-week treatment phase where ISB830 will be administered every other week (q2w) subcutaneously (SC). The primary endpoint of the study will be assessed at the end of the blinded treatment period at Week 16.

Subject eligibility will be assessed during screening, which will occur within 28 days prior to randomization. During the screening period, treatments for AD will be withdrawn or modified for the subject as defined in Table 5 in the protocol. Subjects may be re-screened once (within or outside of the screening period) if they fail the screening evaluation. All screening procedures will be repeated during rescreening.

Subjects who continue to meet eligibility criteria will undergo Day 1/baseline (predose) assessments and will be randomized to equal groups of approximately 78 subjects each.

Subjects will receive SC injections of ISB 830, or corresponding placebo. A total of 27 doses (ISB 830 or placebo) will be administered q2w.

During the blinded treatment phase each subject will receive a dose on Day 1 and q2w starting from Day 15 through Week 14, according to the following treatment assignment below:

Study Part 1:

- Group 1: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume), starting at Day 15 (Week 2).
- Group 2: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by dosing every 4 weeks (q4w) of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted]) will be administered q4w starting at Day 15 (Week 2).
- Group 3: Dose of [redacted] ISB 830 (2 SC injections each containing [redacted] volume) on Day 1, followed by q4w dosing of [redacted] ISB 830 (1 SC injection containing [redacted] volume) starting at Day 29. In order to maintain blinding, placebo (1 SC injection of [redacted]) will be administered q4w starting at Day 15 (Week 2).
- Group 4: Dose of placebo (2 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (1 SC injection of [redacted]) starting at Day 15 (Week 2).

Study Part 2:

- Group 5: Dose of [redacted] ISB 830 (4 SC injections each containing [redacted] volume) on Day 1, followed by q2w dosing of [redacted] ISB 830 (2 SC injections containing [redacted] volume), starting at Day 15 (Week 2).
- Group 6: Dose of placebo (4 SC injections of [redacted] volume) on Day 1, followed by q2w dosing with placebo (2 SC injections of [redacted]) starting at Day 15 (Week 2).

During the blinded treatment phase, all subjects in Groups 1 through 4 will receive a loading dose consisting of 2 SC injections, followed by 7 maintenance doses consisting of 1 SC injection per dose. For Groups 5 and 6, all subjects will receive a loading dose consisting of 4 SC injections, followed by 7 maintenance doses consisting of 2 SC injection per dose, as described in Table 6 Section 10.1 of the Protocol.

During the open-label treatment phase, each subject will receive a dose of ISB 830 SC injection ([redacted]) q2w (consisting of 1 to 2 SC injections per dose, respectively) from Week 16 to Week 52 or until subject withdrawal, as described above and in Table 6 Section 10.1 of the Protocol.

All subjects in Groups 1-4 in the open-label treatment phase will receive [redacted] q2w. All subjects in Groups 5-6 in the open-label treatment phase will receive [redacted] q2w.

Safety assessments, clinical laboratory assessments, vital sign assessments, PK sampling, immunogenicity sampling, and clinical efficacy assessments (IGA and EASI) will be performed by the blinded Investigator and blinded study staff as defined in Table 2 of the protocol (Schedule of Assessments), or until the subject discontinues from the study. Study assessments will be performed at baseline (Day 1) and every week until Week 16. An experimental population PK design will be used for the PK blood sampling. The subjects in the rich PK group will have additional blood sampling between Days 1 to 8 (Week 1), and Days 85 to 92 (Week 12), compared to the sparse PK group. The subjects in the sparse PK group will have widespread sampling with fewer time points for each subject, compared to the rich PK subjects. Approximately 80 rich PK subjects will be randomized (in a 1:1:1:1 ratio) for Groups 1-4, and approximately 40 rich PK subjects will be randomized (in a 1:1 ratio) to Groups 5 and 6. The remaining subjects in the study will be included in the sparse PK group. Blood samples will be collected from the rich and sparse PK subjects according to the respective schedule described in Table 8 of the protocol.

End-of-treatment visits will be conducted on Day 113 (Week 16) for the blinded treatment phase and at Day 379 (Week 54) for the open-label treatment phase for all subjects. After the EOT visit, subjects should continue into the follow-up period and will have a follow-up phone call 4 weeks and 8 weeks after the EOT visit and a final clinic visit 12 weeks after the EOT visit.

Subjects who withdraw consent from the blinded treatment phase prior to Week 16 and are not continuing with treatment and/or entering the open-label treatment phase of the study will undergo the blinded treatment phase EOT visit procedures and enter the follow-up period for the GBR 830-204 study.

Subjects who withdraw consent from open-label treatment phase prior to Week 52 will undergo the open-label treatment phase EOT visit procedures and enter the follow-up period for the GBR 830-204 study.

All subjects continuing in the follow-up period will have a follow-up phone call 4 and 8 weeks after the EOT visit and a final clinic visit 12 weeks after the EOT visit as described in the Table 3 in the protocol follow-up period.

Subjects will be clinically monitored for safety throughout the study, including anaphylactic reactions and/or injection site reactions (ISRs), with monitoring at the study site for 2 hours after the first dose on Day 1 (in the blinded treatment phase) and on Day 113 (Week 16) (first dose in open-label treatment phase) and for 1 hour after dosing at all other visits.

Subjects who receive concomitant therapy with a prohibited medication during the study may have ISB 830 administration temporarily stopped for the duration of the prohibited treatment, including a washout period after last dose of prohibited medication of 4 weeks or 5 half-lives, whichever is longer. Administration of ISB 830 may then be resumed after

the appropriate washout period and following discussion and upon obtaining written approval from the Sponsor's medical monitor.

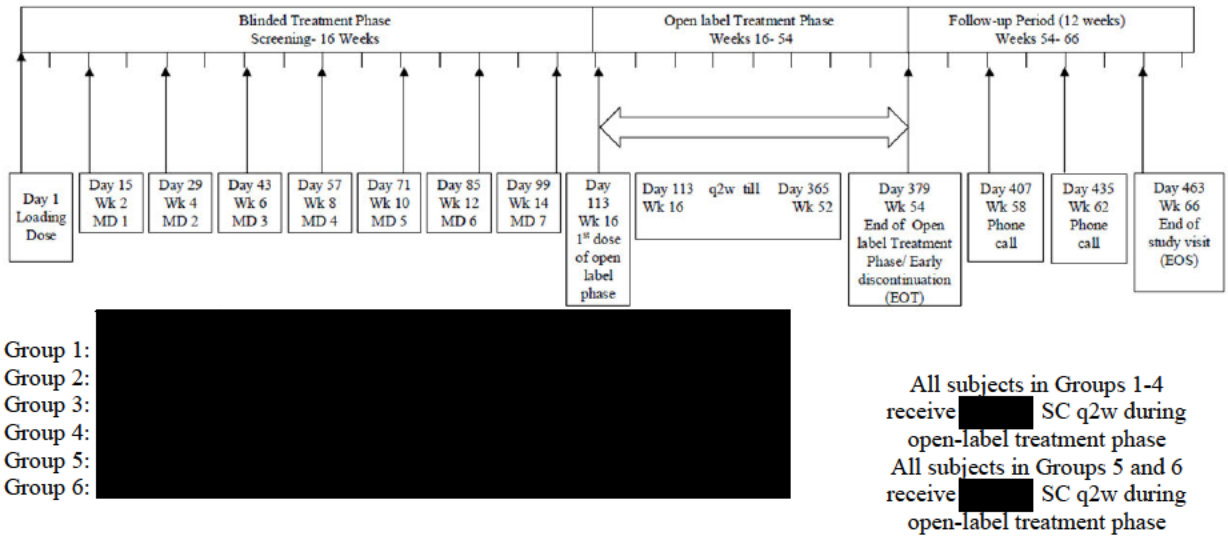
To allow subjects access to the open-label treatment phase of the study, subjects who have completed the GBR 830-204 study prior to implementation of the amendment that includes the open-label phase (e.g., Protocol Amendment 3 (version 4.0) and/or Amendment 6 (version 7.0)) or who are in the follow-up phase of the study at the time of implementation of the open-label protocol amendment, may be eligible to participate in the open-label treatment phase of this study. Subjects who have completed the study prior to implementation of the open-label amendment must undergo a modified Screening visit (as per Table 2 in the protocol).

If eligibility criteria are met (with the exception of inclusion criteria 5, 6, 7, 8, 9, 10 and exclusion criteria 1 and 5), subjects will undergo study assessments as per Table 3 in the protocol).

Subjects who are in the follow-up period of GBR 830-204 at the time the open-label protocol amendment is implemented must complete their follow-up period and then must undergo a modified Screening visit (as per Table 2 in the protocol). This includes a complete washout of any concomitant medications and therapies received (as per Table 5 in the protocol) prior to starting the open-label treatment phase of the study.

See Figure 1 for a schematic diagram of the study design and Table 2 and Table 3 in the protocol for the Schedule of Assessments. The endpoints to be measured in this study are described in Section 3.2.

Figure 1: Study Design



LD = Loading Dose; MD = Maintenance Dose; Wk = Week; q2w= Every 2 weeks; q4w=Every 4 weeks; SC=subcutaneous

4.2. Definition of Study Drugs

Table 4 in the protocol provides a description of the study drug (double-blind ISB 830 and placebo) to be used in the study.

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

[redacted]

4.3.2. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

4.3.3. Enrollment of Additional Subjects

Special considerations have been added to the protocol based on the issues arising from the SARS-CoV-2/COVID-19 pandemic. During the blinded dosing period for Part 2 (ie, prior to completion of the Week 16 visit), any randomized subject who terminates study participation or who misses 2 or more consecutive doses of study drug (even if continuing with study participation) or misses any part of the primary endpoint assessments at Week 16, as a result of pandemic-related reasons, may not be counted against the total number of subjects targeted (N=156 for Part 2 of the study). For each of these cases, a new subject may be screened and randomized, to allow an evaluable number of subjects for the Week 16 primary endpoint. The new subjects in screening will receive new subject numbers and new treatment assignments as per the current randomization schedule in the protocol.

Additional subjects will only be added in response to the number of subjects who meet the above criteria, as a result of pandemic-related issues. Randomized subjects who discontinue study participation or miss consecutive doses or the Week 16 primary endpoint assessments for non- pandemic related reasons, or who have study drug or study visit issues after completing their Week 16 visit, will not trigger the screening of additional subjects.

4.4. Randomization

Randomization numbers will be issued centrally using interactive voice response system (IVRS)/interactive web response system (IWRS). Subjects who meet all eligibility criteria will be randomized on Day 1 using the IVRS/IWRS system and allocated a randomization number prior to receiving the first dose of study drug.

Randomized subjects will be stratified by the IVRS/IWRS based on disease severity (moderate/severe), geographic region (North America (NAm)/European Union (EU)) as prognostic factors, and subjects consenting to rich PK sampling (Yes/No) to ensure balance of treatment groups within each stratum. Randomized subjects who terminate their study participation for any reason, regardless of whether study drug has been taken or not, will retain their randomization number. The randomization scheme will be stored within the IVRS/IWRS database until unblinding of this study is requested. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

4.5. Clinical Assessments

4.5.1. Efficacy Assessments

- The Eczema Area and Severity Index (EASI) is a validated measure used in clinical practice and clinical studies to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the Investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head/neck, trunk(including genital area), upper limbs, and lower limbs (including buttocks) and converted to a score of 0 to 6 (Hanifin et al, 2001). The EASI will be collected in the electronic Case Report Forms (eCRF) and EASI score will be calculated in the eCRF as follows:

Body Region	EASI Score
Head/Neck (H)	(E + I + Ex + L) x Area x 0.1
Upper limbs (UL)	(E + I + Ex + L) x Area x 0.2
Trunk (T)	(E + I + Ex + L) x Area x 0.3
Lower limbs (LL)	(E + I + Ex + L) x Area x 0.4
EASI score	Sum of the above 4 body region scores

The degree of severity of each sign (E = erythema, I = induration/papulation, Ex = excoriation, L = lichenification) in each of the 4 body regions is evaluated based on a scale ranging from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe), with half points allowed. Area (the affected body area) is defined as follows: 0= 0%; 1=1-9%; 2=10-29%; 3=30-49%; 4=50-69%; 5=70-89%; 6=90-100%. Among the 4 zones, trunk includes the genital area, and lower limbs include the buttocks.

- The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA will be collected in the eCRF.

IGA Score	Definition
0 = Clear	No inflammatory sign of atopic dermatitis

1 = Almost clear	Just perceptible erythema and just perceptible papulation/infiltration; Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration; Visible detectible, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration; Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration; Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

- The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and intensity of AD. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The intensity of 6 specific symptoms of AD is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3), (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the subject or relative on a visual analogue scale (VAS), where 0 is no pruritis (or sleep-loss) and 10 is the worst imaginable pruritis (or sleep-loss). This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C (Kunz et al, 1997) and the maximum of SCORAD score is 103. The SCORAD will be collected in the eCRF. If SCORAD uses a non-10cm VAS scale line, the measurement will be converted to 10cm VAS scale line using a standard ratio.
- For Pruritus NRS subjects will respond to the following question, "On a scale of 0 – 10, with 0 being no itch and 10 being the worst itch imaginable, how would you rate your worst degree of itch during the previous 24 hours?". The Pruritis NRS will be assessed and recorded by the subject once per day in the morning, ideally at the same time; and reviewed by study staff at each clinic visit. Baseline Pruritus NRS average score for maximum itch intensity will be determined based on the average of daily Pruritus NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding) randomization. A minimum of 3 daily scores out of the 7 days is required to calculate the baseline average score. For subjects who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening).
- The DLQI is a subject-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work, and school personal relationships and treatment. Response categories include "a little," "a lot," and "very much" with corresponding scores of 1, 2, and 3, respectively; "a little ," "not relevant" responses are scored as "0." Totals range from 0 to 30 (i.e., from less to more impairment), and a 5point change from baseline is considered clinically relevant (Finlay and Khan, 1994; Basra et al, 2008).
- For GISS individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) will be rated globally (i.e., each assessed for the whole

body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria. The GISS will be collected in the eCRF.

- Body Surface Area (BSA) affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]), and will be reported as a percentage of all major body sections combined. The BSA will be collected in the eCRF.
- The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state (Zigmond and Snaith, 1983; Hermann, 1997). The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. At a given visit, there must be responses to at least 6 out of 7 questions within each sub-scale of anxiety and depression. If fewer than 6 responses, then the sub-scale will be set to missing
- The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults (Charman et al, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (i.e., 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.
- The EQ-5D is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D consists of 2 parts: the descriptive system and the EQ visual analogue scale (EQVAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels of perceived problems: "no problem" (level 1), "some problems" (level 2), "extreme problems" (level 3). The VAS scale is a 100-point scale with endpoints ranging from 100 – "best imaginable health state" to 0-"worst imaginable health state".
- The ACQ-5 is a 5-question version of the Juniper ACQ that is a validated questionnaire to evaluate asthma control. The questionnaire will be administered only to the subset of subjects with a medical history of asthma. The ACQ-5 will be collected in the eCRF.
- The SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on quality of life (QoL). The questionnaire will be administered only to a subset of subjects with chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (eg, with chronic rhinitis/ rhinosinusitis, nasal polyps, allergic rhinitis).
- For Patient Global Assessment (PGA) of Disease subjects will rate their overall wellbeing based on a 5-point Likert scale from poor to excellent. Subjects will be asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: "Poor=1"; "Fair=2"; "Good=3"; "Very Good=4"; "Excellent=5."
- For Patient Global Assessment (PGA) of Treatment subjects will rate their satisfaction with the study treatment based on a 5-point Likert scale from poor to excellent. Subjects will be

asked: “How would you rate the way your eczema responded to the study medication?” Response choices are: “Poor=1”; “Fair=2”; “Good=3”; “Very Good=4”; “Excellent=5.”

- For assessment of Sick Leave and/or Missed School Days subjects who are employed or enrolled in school will be asked to report the number of sick leave and/or missed work/school days due to AD (e.g. vs due to an accident) in the last 4 weeks.

4.5.2. Pharmacokinetic Assessments

Blood samples (3.5 mL each) will be collected from both rich and sparse PK groups at appropriate time points defined in Table 2 and 3, and Table 8 in the protocol. Serum concentrations of ISB830 in these samples will be quantified using a validated enzyme-linked immunosorbent assay (ELISA) method. Serum concentration data from both rich PK and sparse PK group from the blinded treatment will be used to derive PK parameters, as appropriate. In the blinded phase of the study, only the serum sample from subjects, belonging to treatment arms that received ISB830 will be analyzed. In open-label phase of the study, PK samples from all subjects will be analyzed.

4.5.3. Immunogenicity Assessments

Blood samples (5 mL) will be collected from all subjects at appropriate time points defined in Table 2, Table 3 and Table 8 in the protocol, to detect the presence of ADA to ISB830, as per procedures similar to collection of PK samples. Antibodies generated against ISB830 will be detected and confirmed using a validated ECLIA method. Details of sample collection, processing and storage and shipment to the bioanalytical laboratory will be outlined in a separate laboratory manual.

4.5.4. Safety Assessments

Safety and tolerability of ISB 830 will be assessed, including adverse event (AE); SAEs; TEAE; anaphylactic events and injection site reactions (ISR); vital signs; physical examinations; electrocardiograms (ECGs); and clinical laboratory parameters, as detailed in the Schedule of Assessments (Table 2 and Table 3) of the protocol.

Guidance will be given to the investigator for the criteria to be used to assess anaphylaxis (Sampson et al, 2006). Injection site reactions will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, 2010).

Stopping/discontinuation/withdrawal criteria are listed in Section 8.3 of the protocol.

In case of premature discontinuation, the reason and their cause must be documented. All appropriate assessments should be conducted at the EOT visits. If the withdrawal is due to an adverse event (AE), the AE should be monitored until it is resolved, stabilizes or has returned to a status that was prior to the AE.

4.6. Changes in the SAP Compared to the Study Protocol

- For the efficacy endpoints (EASI-75 and IGA) stated below, “secondary efficacy endpoints” have been changed to “key secondary efficacy endpoints”
  - Proportion of subjects with EASI-75 (≥75% improvement from baseline) at Week 16

  - Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline >2 points at Week 16

- Protocol section 15.6 “The efficacy results from these 2 parts of the study will be kept separate. However, the safety results will be presented side by side.” has been changed to “The efficacy and safety results from these 2 parts of the study will be kept separate.”
- For Vital Signs, “Shift tables will present changes from baseline (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.” has been changed to “Shift tables will present changes from baseline (categorized as normal; abnormal) to end-of-treatment.”
- For ECG, “Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.” has been changed to “Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal) to end-of-treatment.”
- Protocol section 15.2.4, ‘The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAS population who received ISB 830 and for whom sufficient serum concentration data are available to facilitate derivation of PK parameters, do not have any major protocol deviation, and for whom the time of dosing and the time of sampling are known.’ has been changed to ‘The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAS population who received ISB 830 having no major protocol deviation affecting PK and for whom at least one sample with detectable plasma concentration data is available and for whom the time of dosing and the time of sampling are known.

5. PLANNED ANALYSES

5.1. Interim Analyses

No interim analyses are planned for this study.

5.2. Data Safety Monitoring Board

This study will institute a data safety monitoring board (DSMB) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DSMB will monitor subject safety by formally reviewing accumulated safety data by treatment group at least twice during the study but may require additional review as per DSMB charter. The blinded and unblinded outputs will be submitted to the DSMB as outlined in the DSMB charter.

5.3. Primary Analyses

All planned analyses will be carried out once the clinical database lock (DBL) has taken place. Once this has been achieved, unblinding will occur and the analyses will be performed.

Parts 1 and 2 are two independent parts of the study protocol and will therefore be analyzed separately. That is, upon completion of the double-blind period of Part 1, the database will be partially locked. The data will be analyzed and the topline results (TLR) will be determined.

Similar activities will take place upon the completion of the double-blind period of Part 2.

For Part 1 of the study, Group 1 (ISB [redacted] loading dose/[redacted] q2w maintenance), Group 2 (ISB [redacted] loading dose/[redacted] q4w maintenance) and Group 3 (ISB [redacted] loading dose/[redacted] q4w maintenance) will be compared to the corresponding placebo arm (Group 4).

For Part 2 of the study, Group 5 (ISB [redacted] loading dose/[redacted] q2w maintenance) will be compared to the corresponding placebo arm (Group 6) using the same statistical methods used in the analysis of the first part of the study.

There are two primary analyses locks for the study: Part 1 DBL1 and Part 2 DBL2.

5.4. Final Analyses

All the data until the end of the study will be locked (DBL3) and analyzed for final analyses. Final analyses will supersede any earlier TLFs. It will consist of blinded and open-label treatment phase for Part 1 and Part 2 of the study as detailed below. The outputs will be generated as per the Appendices 'Table, Listing, Figure (TLF Shell)'. Listings will be presented for all Part 1 and Part 2 data.

Part 1 and Part 2 tables and/or figures will be generated for,

- Week 54: Efficacy and Safety
- PK concentration Open-label
- Study Population
- Week 66 or End of Study (EOS) follow-up assessment for the primary and key secondary end points (percentage change from baseline in EASI score, EASI-75 and IGA) for completers and non-completers/early discontinued subjects

Part 1 adhoc tables and/or figures will be generated for,

- Week 16 Efficacy (format: table number suffix '.ah' and table title prefix 'Adhoc Analysis' with footnote 'Adhoc analysis considering the rescue medication censoring ')

Part 1 and Part 2 re-runs of tables will be generated for,

- Week 16 Safety tables (AE and labs), ECG and Study Population (format: table number suffix '.r' and table title prefix 'Re-run:' with footnote 'Re-run: Due to data change after Part 1 database lock the TLFs from Part 1 have been re-run' or with footnote 'Re-run: Due to data change after Part 2 database lock the TLFs from Part 2 have been re-run').

Part 2 re-run of table will be generated for,

- Week 16 Efficacy of NRS (format: table number suffix '.r' and table title prefix 'Re-run:' with footnote 'Re-run: Due to data change after Part 2 database lock the TLFs from Part 2 have been re-run').

The screening, demographic, baseline, PK parameters and week 16 tables and figures will not be generated for Part 1 and Part 2 unless specified for re-runs or adhoc.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. General Summary Table and Individual Subject Data Listing Considerations

Subject number when broken down consists of the site number and 3 digits sequential number. Study visits will be labeled in Electronic Data Capture (EDC) as Screening, Baseline (Day 1/Week 0), Day 8/Week1, Day 15/Week 2, Day 22/Week 3, Day 29/Week 4, Day 43/Week 6, Day 57/Week 8, Day 71/Week 10, Day 85/week 12, Day 99/Week 14 and Day 113/Week 16 (end of blinded treatment phase and start of open-label phase), Day 127/Week 18, Day 141/Week 20, Day 155/Week 22, Day 169/Week 24, Day 183/Week 26, Day 197/Week 28, Day 379/Week 54 (end of open-label phase) as well as Day 405/Week 58, Day 435/Week 62, Day 463/Week 66 (end of follow up and Unscheduled. When required, the time of the scheduled assessment will be included. In general, listings will be sorted and presented by treatment and subject number.

The following treatment levels will be used for all tables, figures, and listings in the order below:

Part	Treatment Group	Treatment Level
Part 1	Treatment Group 1	ISB830-1
	Treatment Group 2	ISB830-2
	Treatment Group 3	ISB830-3
		ISB830-Total
	Treatment Group 4	Placebo-1
Part 2	Treatment Group 5	ISB830-5
	Treatment Group 6	Placebo-2

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Tables, figures and listings are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. Additional tables, figures and listings will be generated, as needed, following the data analysis.

6.3. Data Management

Data from the study will be managed by the Sponsor's Clinical Research Operations group or designee. The Investigator will allow representatives of the Sponsor, regulatory agencies, and their designees to inspect all study documents (including, but not limited to, consent forms, IP accountability forms, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals) and pertinent hospital or clinic records for confirmation of data throughout and after completion of the study. Monitoring visits will be conducted as needed during the course of the

study. A complete review of source documentation of key efficacy and safety data will be conducted at each monitoring visit for verification that all information recorded in the eCRF accurately reflects the data recorded in the subject's source documents. All data verification, using hospital or clinic records, will be performed respecting subject confidentiality and will be carried out in accordance with SOPs. All subject data generated during the study will be recorded and transcribed into a database. The final authorization of the CRF/eCRF data is the Investigator Signature Form. This form must be approved by the Principal Investigator to signify that he/she has reviewed the CRF/eCRF, including all laboratory and safety assessments, and that all of the data therein is complete and accurate. The data will be reviewed to ensure that the forms were completed properly. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

All tables, figures and listings will be produced using SAS® statistical software Version 9.3 or higher, unless otherwise noted in a secure and validated environment. All tables and listings will be produced in RTF format and all outputs will be independently checked for consistency, integrity in accordance with standard Parexel procedures.

6.4. Data Presentation Conventions

- Continuous data will be summarized in terms of the mean, SD, median, minimum, maximum, and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum, and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database where applicable. The SD will be reported to two more decimal places than the raw data recorded in the database where applicable. In general, the maximum number of decimal places reported shall be four for any summary statistic.
- Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point, frequency counts, and percentages. Any planned collapsing of categories will be detailed in the corresponding sections of this SAP and within the data displays. The percentages will be presented to one decimal place and will not be presented for zero counts.
- Percentages will be calculated using N as the denominator.
- Changes from baseline in categorical data will be summarized using shift tables where appropriate.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be decimal aligned.
- P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as “<0.001” and p-values greater than 0.999 will be presented as “>0.999.”

- Confidence intervals will be presented to one more decimal place than the raw data where applicable.
- When change from baseline is assessed at a post-baseline visit, unless otherwise specified, only patients with both baseline and post-baseline measurements will be included in the analysis. If baseline or post-baseline value is missing for a patient, then the change from baseline will be set to missing.
- For patients who withdraw, all data will be reported prior to the point of withdrawal in line with the population definitions and the specified analysis.
- A table, figure, listing is to be generated for any required item where no data is available or reported, with either a table or listing stating "No Data Available" or "No Data Reported," or print a 1 line message indicating there was no report data available: "No Data Available For This Report."

6.5. Analysis Populations

Study population is adult males and females (≥ 18 years of age) with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable (e.g. intolerance, other important side effects or safety risks).

6.5.1. Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who are randomized and received at least 1 dose of study medication. Based upon the Intent-to-Treat (ITT) principle, subjects will be analyzed according to the treatment group assigned.

The efficacy summaries and analyses will be based on the FAS population. In the event that a subject is allocated the incorrect study treatment as per the study randomization list, subjects will be summarized and analyzed 'as randomized' (i.e., by randomized treatment group). In the event that a subject is stratified incorrectly, 'randomized stratum' will be used rather than 'actual stratum.'

6.5.2. Per-Protocol Set

The Per Protocol Set (PPS) consists of all FAS subjects who have no major protocol deviations of eligibility or on-treatment study conduct.

For the primary and key secondary efficacy endpoints, analysis will be performed on the PPS to assess the robustness of the study conclusions to the choice of analysis population. Subjects will be included in the analysis according to the treatment 'as randomized'.

6.5.3. Safety Analysis Set

The Safety Analysis Set (SAS) consists of all subjects who were randomized and took at least 1 dose of study medication. Subjects will be analyzed according to the treatment they received. Randomized subjects will only be excluded if there is clear, documented evidence that the subject did not receive any study drug injection.

6.5.4. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PKAS) consists of the subset of the SAS population who received ISB 830 having no major protocol deviation affecting PK and for whom at least one sample with detectable plasma concentration data is available and for whom the time of dosing and the time of sampling are known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokinetist.

6.5.5. Subjects Not Impacted by the Pandemic

The subjects not impacted by the pandemic excludes subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic. This subset will be analyzed for Part 2 of the study.

6.6. Baseline Definition

Baseline is defined as the last non-missing result prior to administration of the first dose of study medication during blinded treatment phase.

The Baseline value for primary and secondary efficacy evaluations, laboratory data, physical examination, and vital signs will be defined as the visit of Day 1 measurement. If this measurement is not available, the visit of D-28 to D-1 measurement will be used as the baseline value (including the assessment performed in the unscheduled visits).

Baseline pruritus NRS average score for maximum itch intensity will be based on the average of daily NRS scores for maximum itch intensity ≥ 3 over the previous 24 hours (the daily score ranges from 0 to 10). A minimum of 3 daily scores out of the 7 days is required to calculate the baseline average score. For subjects who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum during for screening.

6.7. Derived and Transformed Data

The derived and transformed data are provided as follows.

- Treatment duration of study drug exposure in days will be derived as:
- Duration = date of the last dose - date of the first dose + 1
- Study day will be derived as follows:
    - If the date of interest occurs on or after the randomization date:

      Study day = date of interest – randomization date + 1

- If the date of interest occurs before the randomization date:

  Study day = date of interest – randomization date

- There is no study Day 0.

- Change from baseline will be calculated as
  - Change from baseline = post baseline measurement – baseline measurement
- Percent change from baseline is calculated as
- (Change from baseline/baseline measurement) × 100
- Body mass index (BMI) will be computed using the formula:
  - BMI = (weight in kilograms)/ (height in m)^2

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline are set to missing as well. If baseline measurement is missing, the percent change from baseline is also set to missing.

6.7.1. Visit Windows

Table 2: Visits (Days)

contains a list of visits in the study period. Data will be analyzed based on the nominal visit/time.

Table 2: Visits (Days)

Study Period	Visit Description
Screening	
Blinded treatment phase	Day 1 (Week 0)
	Day 8 (Week 1)
	Day 15 (Week 2)
	Day 22 (Week 3)
	Day 29 (Week 4)
	Day 43 (Week 6)
	Day 57 (Week 8)
	Day 71 (Week 10)
	Day 85 (Week 12)
	Day 99 (Week 14)
EOT (Blinded treatment phase)	Day 113 (Week 16)
Open-label phase	Day 113 (Week 16)
	Day 127 (Week 18)
	Day 141 (Week 20)
	Day 155 (Week 22)
	Day 169 (Week 24)
	Day 183 (Week 26)
	Day 197 (Week 28)
	Long-term Day 211 to 365

	(Week 30 to Week 52)
EOT (Open-label phase)	Day 379 (Week 54)
Follow-up phase	Day 407 (Week 58)
	Day 435 (Week 62)
EOS	Day 463 (Week 66)

These analysis visits will be used in the calculations for all week-based parameters collected on subject's diary (e.g., pruritus NRS). Other non-diary data, such as IGA, EASI, BSA, SCORAD, GISS, POEM, DLQI, HADS, EQ5D, missed work/school day, vital signs, body weight, clinical laboratory assessments will be analyzed according to actual scheduled visits.

For efficacy and safety data (except clinical laboratory assessments), where two or more assessments (include both scheduled and unscheduled assessments) are available for the same visit interval, the one closest to the target visit date will be used for the summary and analyses.

For clinical laboratory assessments, if repeated measurements are taken for either time point (scheduled visit), then the last measurement will be used for the value for that time point.

6.7.2. Unscheduled Assessments

Unscheduled assessments (laboratory data, ECG or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not in summaries.

6.7.3. Visit Re-mapping

Assessment reported in End of treatment (EOT) blinded or open-label visits for early discontinued subjects only will be mapped to the next closest scheduled visit according to protocol (Table 2 or 3). Some assessments follow the midpoint algorithm visits re-mapping while others do not.

6.7.3.1. Algorithm

The 'midpoint algorithm' was used as per scheduled protocol visit for the corresponding assessment as per SoA (protocol Table2 and Table3). Find the mid-point between two scheduled protocol visits. If the date of assessment is before the mid-point, map to the earlier visit; otherwise map to the later visit. Unless, the earlier scheduled protocol visit is present, then map it to the next scheduled protocol visit. The different assessments as per their scheduled protocol visits (SoA) are presented:

- DLQI, PATIENT-ORIENTED ECZEMA MEASURE, EQ-5D-3L, HADS, GLOBAL INDIVIDUAL SIGNS SCORE, INVESTIGATOR'S GLOBAL ASSESSMENT FOR SKIN LESIONS, BODY SURFACE AREA IN ATOPIC DERMATITIS, ECZEMA AREA AND SEVERITY INDEX, SCORING OF ATOPIC DERMATITIS
- VS, PE
- LB
- GLOBAL ASSESSMENT OF DISEASE
- GLOBAL ASSESSMENT OF TREATMENT
- ASSESSMENT OF SICK LEAVE OR MISSED SCHOOL DAYS
- IS (Immunogenicity)

For example, if EASI assessment has EOT as day x=96. The midpoint between Week 12 Day 85 and Week 16 Day 113 is (113+85)/2=99. If we have x<99 then we will map it to week12 Day 85; if we have x>=99 then we will map it to week 16 Day 113. Since 96<99 so we will remap it to week 12 for EASI. Unless, the earlier scheduled protocol visit is present (week 12), then map it to the next scheduled protocol visit (week 16).

For ACQ, SNOT (CHRONIC RHINITIS/RHINOSINUSITIS) and ECG assessments, midpoint algorithm will not be used since these assessments only have Day1 and Day113 protocol scheduled visits. PK domain will also not use midpoint algorithm because they are not by visits but are by time point (Table 8 of the protocol).

End of Study Visit is assigned as "Day 463 (Week 66)" for completers. Early discontinued subjects will not be re-mapped.

For NRS, the following window will be followed:

Table 3: Numerical Rating Scale

Analysis Visit	Visit Window Start	Visit Window End
Baseline	-7	-1
Day 8 (Week 1)	1	8
Day 15 (Week 2)	9	15
Day 22 (Week 3)	16	22
Day 29 (Week 4)	23	29
Day 37 (Week 5)	30	36
Day 43 (Week 6)	37	43
Day 50 (Week 7)	44	50
Day 57 (Week 8)	51	57
Day 64 (Week 9)	58	64
Day 71 (Week 10)	65	71
Day 78 (Week 11)	72	78
Day 85 (Week 12)	79	85
Day 92 (Week 13)	86	92
Day 99 (Week 14)	93	99
Day 106 (Week 15)	100	106
Day 113 (Week 16)	Prior to or on 7 days from End of blinded treatment date for the respective subject	

For assessment recorded after End of Blinded Treatment, calculate week from End of Blinded Treatment Date, and start with Week 17. Add one week by 7 days.

6.8. Handling of Missing Data

6.8.1. Missing Primary and Secondary Endpoints

To test the robustness of Mixed-effect Model for Repeated Measures (MMRM) model for the primary endpoint, sensitivity analyses using tipping point approach will be conducted. In addition, the primary endpoint will be analyzed using the complete dataset (patients who

complete the week 16 and had EASI measurement). To assess the robustness of the results in the Part 2 of the study, the primary endpoint analysis using sensitivity analyses tipping point and complete dataset will be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

Sensitivity Analyses using Last Observation Carried Forward (LOCF) method and Observed Data approach will be used for key secondary endpoints (EASI-75 and IGA), analyzed using CMH test. Also, the sensitivity analyses for key secondary endpoints will be conducted on the subjects not impacted by the pandemic.

6.8.2. Missing Start and Stop Dates for Prior and Concomitant Medication

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication starts and stop dates will be imputed as follows:

- If year and month are present and day is missing, then set day to first day of month for start date and set day to last day of month for end date.
- If year and day are present and month is missing, then set month to January for start date, and set month to December for end date.
- If year is present and month and day are missing, then set month and day to January 1 for start date and set month and day to December 31 for end date.
- Completely missing date will not be imputed.

The partial dates will be provided as such in the subject data listings (with the imputed dates).

When imputing a start date, ensure that the new imputed date is sensible i.e. it is before the end date of prior and concomitant medications.

6.8.3. Missing Start and Stop Dates for Adverse Events

Due diligence will be done to obtain accurate AE information. If all planned methods to obtain accurate time AE information have failed, missing and partial AE onset and end dates will be imputed. Imputed dates will be flagged in the individual supportive subject listings. Unless otherwise specified, the following conventions will be used:

Missing and Partial AE onset dates:

- If onset date is completely missing, then onset date is set to date of first dose.
- If onset year is present and

  - month and day are missing:
    - If onset year = year of first dose, then set onset date to date of first dose.
    - If onset year < year of first dose, then set onset month and day to December 31st.
    - If onset year > year of first dose, then set onset month and day to January 1st.

  - month is missing:
    - If onset year = year of first dose, then set onset date to date of first dose.
    - If onset year < year of first dose, then set onset month to December.

  - If onset year > year of first dose, then set onset month to January.

- If onset month and year are present and day is missing:

  - If onset year = year of first dose and

    - onset month = month of first dose then set onset date to date of first dose.
    - onset month < month of first dose then set onset date to last day of month.
    - onset month > month of first dose then set onset date to 1st day of month.

  - If onset year < year of first dose, then set onset date to last day of month.

  - If onset year > year of first dose, then set onset date to 1st day of month.

- For all other cases, set onset date to date of first dose.

Missing and Partial AE end dates:

- If end date is completely missing, end date is not imputed and the AE is flagged as "ongoing".
- If year is present and

  - month and day are missing:

    - If year = year of last dose, then set end date to the date of last dose.
    - If year < year of last dose, then set end month and day to December 31st.
    - If year > year of last dose, then set end month and day to January 1st.

  - month is missing:

    - If year = year of last dose, then set end date to date of last dose.
    - If year < year of last dose, then set end month to December.
    - If year > year of last dose, then set end month to January.

- If month and year are present and day is missing:

  - If year = year of last dose and

    - month = month of last dose then set day to day of last dose.
    - month < month of last dose then set day to last day of month.
    - month > month of last dose then set day to 1st day of month.

  - If year < year of last dose, then set end date to last day of the month.

  - If year > year of last dose, then set end date to 1st day of month.

- For all other cases, set end date to date of last dose.
- Screen failures is collected in EDC and will be a part of SDTM. Screen failure data is not analyzed and will not be included in the ADaM except for demographics (ADSL) and inclusion/exclusion criteria (ADIE).

7. STUDY POPULATION

7.1. Subjects Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to end of study participation. Summaries of subject disposition will be presented by treatment arm and over-all as follows:

- Number and percentage of subjects randomized
- Number and percentage of subjects completed during the blinded treatment phase
- Number and percentage of subjects completed during open-label phase
- Number and percentage of subjects discontinued from the study and reasons during the blinded treatment phase
- Number and percentage of subjects discontinued from the study and reasons during open-label phase
- Number and percentage of subjects who withdrew early from the follow-up period of the study (including reasons for early withdrawal)
- By-subject listings of enrollment details (last contact date, reason of screened failure), randomization details (randomization number, planned arm, stratification IGA, region), visit dates, and withdrawal details (including reason for discontinuation and duration of treatment prior to discontinuation) will also be provided.

7.2. Screen Failures

The number and percentage of subjects who were screened for the study (enrolled subjects, i.e., those who signed informed consent) and reasons for screen failure will be summarized.

7.3. Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as ‘minor’ or ‘major.’ Major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject’s right, safety, well-being, and/or the validity of the data for analysis. Minor deviations include all deviations from the protocol excluding those considered as major. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis population (see Section 6.5), both including and excluding data potentially affected by major protocol deviations. Major protocol deviations that will lead to the exclusion of a subject from the PPS will be identified. The final determination of major protocol deviations and the exclusion of subjects from each of the analysis populations will be made prior to database lock. Latest PD specification will be followed.

Major protocol deviations may include:

- Subjects who did not satisfy the inclusion/exclusion criteria that may have a significant influence on efficacy.

- Subjects who did not provide inform consent
- Subjects who used prohibited medications (prior and/or concomitant) that may have a significant influence on efficacy.
- Subjects who did not comply with IP administration/study treatment including overall treatment compliance <80% or >100%
- Subjects who violated procedure/tests
- Subjects who missed visit schedule including out of window
- Subjects who had their blinded randomization code broken.
- Subjects not treated with the treatment assigned at randomization, but wrongly treated in another treatment group.

The following protocol deviation summaries will be provided:

- Number and percentage of subjects with a major protocol deviation by type of deviation
- Number and percentage of subjects with a major protocol deviation resulting in exclusion of subjects from the PPS analysis by type of deviation

A by-subject listing of protocol deviations will be provided along with COVID-19 Impact listing (SAP Section 7.8).

Upon database release, protocol deviation and analysis population outputs will be produced and will be reviewed by the Sponsor. An analysis population classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to database lock and unblinding and will be documented and approved by the Sponsor.

7.4. Demographic and Other Baseline Characteristics

The following demographic characteristics will be summarized for subjects in the FAS population by treatment arm:

- Age (years, a continuous variable) at baseline
- Age categorization ((≥18 - <65, ≥65 years, a categorical variable) at baseline
- Sex (Male, Female, a categorical variable)
- Race (White, Black/African American, Asian, American Indian/Alaska Native, Hawaiian Native/Other Pacific Islander, Mixed, Other, a categorical variable)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, a categorical variable)
- Region (NAm or EU, a categorical variable)
- Weight at screening (in kilograms, a continuous variable)
- Height at screening (in centimeters, a continuous variable)
- BMI at screening (in kg/m^2, a continuous variable)

- Baseline EASI (a continuous variable)
- Baseline IGA (a categorical variable)
- Baseline BSA (a continuous variable)
- Baseline average and peak pruritus NRS (weekly average during the 7 days prior to Day 1, a continuous variable)
- Number of days with severe pruritus in the past 7 days (Severe Pruritus is ≥ 7 on Pruritus Numerical Rating Scale)
- Total SCORAD (a continuous variable)
- Childbearing potential (female only, childbearing potential or surgically sterilized or postmenopausal, a categorical variable)
- Urine pregnancy test at baseline (Positive or Negative, a categorical variable)
- Smoking status (a categorical variable)
- Time since AD diagnosis (year, a continuous variable)
- Time since AD diagnosis category (<2 years, 2-5 years, or ≥5 years, a categorical variable)
- Skin biopsy results (eosinophilic, non-eosinophilic or other, a categorical variable)

Age will be calculated by IVRS as the number of complete years between a subject's birth date and the date of informed consent.

A summary table for the stratification factor IGA (3 or 4) will be provided.

By-subject listings of demographic data and other baseline characteristics (as summarized above) will be provided.

7.5. Listing of Subject Inclusion and Exclusion Criteria

Subjects who failed any of the inclusion and exclusion criteria will be listed along with the reason. Any subject withdrawal during the study, along with the reason for withdrawal, will be documented in listings.

Failed inclusion/exclusion criteria and withdrawal data will be listed by subject.

7.6. Medical History and Medical Conditions Present at Entry

Recent medical and surgical history (any illness occurring within past 4 weeks), previous medical history, and smoking, alcohol and intakes of drugs of abuse, and history of allergy (*Dermatophagoides farina* (house dust mite), birch oak, cockroach, cat dander, dog dander, and Bermuda grass) will be recorded at the Screening visit.

Medical history will be coded by system organ class (SOC) and preferred term (PT) using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA™) available in EDC at the time of analysis.

The following body systems will be considered:

- Heads, eyes, ears, nose and throat (HEENT)
- Cardiovascular System
- Respiratory System
- Musculoskeletal System
- Dermatological System
- Skin and its appendages
- Lymphatic System
- Gastrointestinal System
- Genitourinary System
- Nervous System
- Endocrine System
- Immunological System
- Allergic Conditions
- Other

A subject listing of all medical /surgical history data will be provided including body system, PT, start and end dates and ongoing status.

7.7. Prior and Concomitant and Rescue Medication

The medications and therapies listed in Table 5 in the protocol are excluded for the designated length of time prior to Baseline (Day 1) and prior to Week 16 (Day 113) for those subjects who completed the study and re-enter only the open-label treatment phase of the study. All restrictions on the medications listed in Table 5 in the protocol are applicable for the entire duration of the study. Other concomitant medication that the subject receives on a regular basis may continue, if in the opinion of the Investigator, it does not put the subject at undue risk or does not interfere with the study medications. Rescue treatment may be given for AD (drug or phototherapy or both) based on the opinion of the Investigator, subjects who receive topical rescue treatment (such as topical corticosteroid (TCS), topical calcineurin inhibitor (TCI), crisaborole, or phototherapy) may continue study treatment after appropriate washout.

The following information must be recorded in the EDC system for each concomitant medication: preferred name or trade name, route of administration, start date, stop date, dose level, total daily dose, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the EDC system.

Medications will be assigned to a time period (prior and/or concomitant) as follows:

- If both the start and stop date exist and are before the first dose date of study drug, the medication will be counted as prior.
- If the start date is on or after the first dose date of study drug, the medication will be counted as concomitant.

- If the start date and stop date is on the first dose date of study drug, the medication will be counted as prior.
- If the start date is before the first dose date of study drug and the stop date is after the first dose date of study drug or the medication is continuing, the medication will be counted as concomitant.
- If the start date is missing and the stop date is before the first dose of study drug, the medication will be counted as prior.
- If the start date is missing and the stop date is after the first dose of study drug or the medication is continuing, the medication will be counted as concomitant.
- If the start and stop dates are missing, the medication will be counted as concomitant.

Previous and concomitant medications will be coded using the most recent version of World Health Organization Drug Dictionary (WHODD) available in EDC at the time of analysis. Summaries showing number of subjects and percentage taking each medication will be provided for each Anatomical Therapeutic Chemical (ATC) level 2, level 3 and preferred name by treatment arm. Subjects with more than one procedure in a given ATC will be counted only once in that category. A by-subject listing of all prior and concomitant medication data will also be provided.

7.8. Impact of COVID-19

Pandemic related Impact of COVID-19 will be presented in listing, detailing the category of impact (example: Missed Visit, Missed Assessment, Early termination, Screen Failure, Adverse Event, Withdrawal of consent, Death, Replacement subject).

8. EFFICACY ANALYSES

The primary and secondary efficacy analyses will be conducted for all subjects in the FAS using the treatment arm as assigned. For the primary and key secondary endpoints, the efficacy analysis will be also be performed using the PPS. Line Plots / bar charts will be presented for IGA, EASI and SCORAD.

Part 1 and Part 2 are two independent parts of the study protocol and will therefore be analyzed separately. That is, upon completion of the double-blind period of Part 1, the database will be partially locked. The data will be analyzed and the TLR will be determined. Similar activities will take place upon the completion of the double-blind period of Part 2.

8.1. General Considerations

Data collected in the blinded treatment phase will be used for all efficacy analyses.

- All tests will be 2-sided and at the 5% level of significance unless otherwise stated.
- All endpoints will be summarized over time, by treatment, as appropriate.
- All endpoints will also be listed by treatment and subject.
- The primary and secondary efficacy analyses will be based on FAS.

- The PPS will be used to assess the robustness of the results from the primary and key secondary endpoint.
- Any subject who received a rescue medication for AD (in blinded or open-label phase) will be considered a treatment failure for the purpose of efficacy evaluation.
- Sensitivity analysis (where applicable) will be carried out for Week 16 only and will be based on FAS.
- Unless otherwise stated, 'treatment' refers to treatment dosing regimen group as randomized, rather than based on the actual treatment received.

8.2. Testing Statistical Assumptions Including Comparability at Baseline

All baseline data will be summarized by treatment group using descriptive statistics. No formal hypothesis testing will be conducted. Differences may occur by chance. If there are any clinically meaningful differences identified, analyses may be adjusted to account for these imbalances through inclusion of additional covariates in the statistical models.

8.3. Statement of the Null and Alternate Hypotheses

The following null hypothesis and alternative will be tested for each ISB 830 group and the placebo group.

H_0: There is no treatment difference between ISB 830 and placebo

H_a: There is a treatment difference between ISB 830 and placebo.

Disease severity and region will be the 2 prognostic stratification factors for patient randomization and will be accounted for in the statistical modelling for efficacy.

8.4. Analyses on Subjects Not Impacted by the Pandemic

These analyses are on the subset of subjects not impacted by the pandemic. This subset excludes subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic. This subset will be analyzed for Part 2 of the study.

The primary (percentage change from baseline in EASI score at Week 16) and key secondary efficacy (EASI-75 and IGA) endpoint analyses performed on FAS and PPS will also be performed on this subset. To assess the robustness of the results in the Part 2 of the study, the primary endpoint using sensitivity analyses tipping point and complete dataset will also be conducted on this subset.

8.5. Multiple Comparisons and Multiplicity

Not applicable.

8.6. Analysis of the Primary Efficacy Endpoint

For both Part 1 and Part 2 of the study, the primary endpoint (percentage change from baseline in EASI score at Week 16) will be analyzed using MMRM.

For continuous primary endpoint (percent change from baseline in EASI score at Week 16), a MMRM will be used, which will account for the variance-covariance structure between visits and missing data. This model includes all schedule visits for the response variable. Early discontinuation visit will be mapped to the nearest scheduled visit of the response variable. The fixed effect factors for treatment, randomization strata (region, disease severity), visit as a categorical variable, treatment-by-visit interaction, relevant baseline value and the baseline-by-visit interaction. An unstructured (UN) covariance matrix for repeated measures within a subject will be used to model the within-subject errors in the analysis, unless there are issues related to convergence. If the UN covariance matrix leads to non-convergence, then Akaike's information criterion (AIC) will be used to select the best covariance matrix among autoregressive, compound symmetric, and Toeplitz. The adjusted means for each treatment and the estimated treatment differences for the treatment comparisons will be presented together with 95% confidence intervals (CIs), along with P-values for the treatment comparisons. The adjusted means and estimated treatment differences for the treatment comparisons (each ISB 830 group vs placebo group) will also be plotted, with corresponding 95% CIs.

8.6.1. Sensitivity Analyses of the Primary Efficacy Endpoint

The primary endpoint of percent change from baseline in EASI at Week 16 will be analyzed by sensitivity analyses using tipping point approach. It will be analyzed using the complete dataset (patients who complete the Week 16 and had EASI measurement). It will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

8.6.1.1. Sensitivity Analysis – Tipping Point Approach

The primary endpoint of percent change from baseline in EASI at Week 16 will also be analyzed using a special application of multiple imputation (MI) of missing values known as the tipping point method. The tipping point method assesses the possibility that subjects on active drug with missing values have worse outcomes than subjects on placebo. This sensitivity analysis involves MIs and is also under the missing not at random (MNAR) assumption in which one searches for a tipping point (region) that reverses the study conclusion. This approach is iterative in nature which tests how severe departures from missing at random (MAR) must be in order to overturn conclusions from the primary analysis. If these departures from MAR in order to change the results from statistically significance ($P \leq 0.05$) to statistically insignificance ($P > 0.05$) are deemed to be implausible, the results will be said to be robust to the departure from MAR assumption (Roderick J et al, 2019).

The tipping point approach will be applied to the analysis of the endpoints using the MMRM. In the MMRM, the dependent variable is change from baseline while the covariates are treatment, randomization strata, visit (categorical variable), treatment-by-visit interaction, relevant baseline value and the baseline-by-visit interaction.

The imputation will be done on the missing cases of change from baseline values for ISB830 group. Under the MNAR assumption, the imputed values for observations in ISB830 group will be adjusted directly using a shift parameter. Missing values are imputed under the assumption that the distribution of the missing observations has a lower expected value than that of the observed only by a shift parameter value. The shift parameter represents the delta which is an

incremental adjustment applied to the imputed value of the percent change. If the tipping point is found to be between two increments on the given interval, a subsequent tipping point procedure will be performed using an interval on the neighborhood of the perceived tipping point finer increments for the shift parameter. We start with the delta=0 and increase the delta in increments e.g. if 0.1 is the increment then delta will be 0, 0.1, 0.2 and so on. We will stop at a delta where non-significant p value is achieved. The tipping point report (table) for each pairwise comparison will include values for the LSmeans, the 95% CI, and the p-value for each of the delta value (including 0, until p-values are no longer statistically significant. Depending on applicable increment, display around 5-10 delta values in the table including δ=0 until δ=x.x.). If no tipping point is found, the shift parameter will be made more stringent and the process repeated.

Implementing the tipping point approach includes the following steps with the first 3 steps being the standard MI steps using SAS® 9.4:

a. Generate multiple imputed data sets with a specified shift parameter that adjusts the imputed values for observations in the active treatment groups.
b. The imputed data sets are analyzed using PROC MIXED.
c. The results are then combined for the inference using PROC MIANALYZE.
d. Repeat the step (a)-(c) to obtain the p-value until the significance changes.
e. If needed, repeat the steps (a)-(d) with more stringent shift parameter applied until the direction of the significance changes.

The iteration for each value of the shift parameter will be summarized in a table where the estimated treatment differences for the treatment comparisons will be presented together with 95% CIs for the differences and P-values for the treatment comparisons.

8.6.1.2. Sensitivity Analysis – Complete Data Approach

The primary endpoint of percent change from baseline in EASI at Week 16 will be analyzed with complete dataset (with no missing data) using MMRM similar to Section 8.6. The patients who complete the Week 16 and have an EASI measurement at baseline and Week 16 will be only analyzed. If a subject withdraws from the study before Week 16 or does not have EASI record at baseline or Week 16 then he will not be considered in the analyses.

8.6.1.3. Sensitivity Analysis – Subjects Not Impacted by the Pandemic

To assess the robustness of the results in the Part 2 of the study, the analyses on primary endpoint using MMRM will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic. Additionally, Tipping point and Complete Data approach will be also analyzed on the subjects not impacted by the pandemic.

8.7. Analyses of the Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects with EASI-75 (75% improvement from baseline) at Week 16 (key secondary endpoint) – Binary variable

- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points at Week 16 (key secondary endpoint) – Binary variable
- Proportion of subjects with improvement (reduction) of Pruritus NRS ≥4 from baseline to Week 16 – Binary variable
- Proportion of subjects who achieve an EASI-50 (50% improvement from baseline) response from baseline through Week 16 – Binary variable
- Change in SCORAD from baseline through Week 16 – Continuous variable
- Change in the DLQI from baseline through Week 16 – Continuous variable
- Change in GISS (erythema, infiltration/population, excoriations, lichenification) from baseline through Week 16 – Continuous variable
- Change in HADS from baseline through Week 16 – Continuous variable
- Change in POEM from baseline through Week 16 – Continuous variable
- Absolute and percent change in PGA of Disease from baseline through Week 16 – Continuous variable
- Absolute and percent change in PGA of Treatment from baseline through Week 16 – Continuous variable
- Assessment of sick leave and/or missed school days through Week 16 - Continuous variable

The key secondary endpoints are the proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and IGA reduction from baseline of ≥2 points at Week 16 and the proportion of subjects achieving EASI-75 at Week 16. The analyses will be based on the stratified Cochran-Mantel-Haenszel (CMH) test where randomization strata (region, disease severity) will be used as stratification variables. Pairwise treatment comparisons will be made based on the CMH test using the P-value for the general association. The odd ratio and associated confidence interval based on Wald test will be provided. The subjects with both IGA 0 or 1 (on a 5-point scale) and IGA reduction from baseline of ≥2 points at Week 16 will be considered as Responders. Any subject who receives protocol-specified rescue medication during the blinded treatment period or withdraws from the study before Week 16, will be considered a Non-Responder. Also, any subject who is missing a Week 16 efficacy assessment will be considered a Non-Responder.

The key secondary endpoint EASI-75 will be analyzed similarly.

For all other binary endpoints Pruritus NRS and EASI-50, the efficacy analysis will also use the Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity) to analyze the categorical secondary endpoints. The FAS will be used for these analyses. The PPS will be used to assess the robustness of the results from the key secondary endpoint (EASI-75 and IGA, respectively). The continuous secondary endpoints will be analyzed using the MMRM model similar to primary endpoint.

8.7.1. Sensitivity Analyses of the Secondary Efficacy Endpoints

Sensitivity analyses using Last Observation Carried Forward (LOCF) method and Observed Data approach will be performed to analyze the key secondary endpoints of IGA and EASI-75. It will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

8.7.1.1. Sensitivity Analysis – LOCF Approach

For the binary secondary endpoints, the efficacy data will be set to missing after rescue medication is used or subject withdrawal before Week 16. The Last Observation Carried Forward (LOCF) method will be used as a sensitivity analysis to determine the status of subjects at Week 16 after censoring for the use of rescue medication or for study withdrawal. This analysis will be conducted to assess the robustness of the secondary endpoints' analyses for IGA and EASI-75 regarding handling of missing data.

For subjects who received a rescue medication for atopic dermatitis (AD) during the blinded treatment period, any assessments present after rescue medication are set to missing, and their last available assessment on or before the rescue medication will be used for imputation. For subjects who did not receive a rescue medication for atopic dermatitis (AD) during the blinded treatment period, and who had missing Week 16 assessment or withdrew before Week 16, their last available assessment before Week 16 will be used for imputation.

8.7.1.2. Sensitivity Analysis – Observed Data Approach

The key secondary endpoints of EASI-75 and IGA will be analyzed using the Observed Data approach by CMH test. All observed data, regardless if rescue medication for atopic dermatitis (AD) during the blinded treatment period was received will be included. Any subject who had missing Week 16 assessment or who withdrew before Week 16 will be considered as Non-Responder.

8.7.1.3. Sensitivity Analysis – Subjects Not Impacted by the Pandemic

To assess the robustness of the results in the Part 2 of the study, the analyses on secondary endpoints (IGA, EASI-75) using CMH test will also be conducted excluding subjects who withdraw from the study or miss 2 or more consecutive doses prior to Week 16 or miss any part of the primary endpoint assessments at Week 16 due to the pandemic.

8.8. Impact-benefit of treatment at follow-up

Impact-benefit of treatment at follow-up will be evaluated for primary and key secondary efficacy assessments at EOS. Descriptive statistics will be presented for the percentage change from baseline in EASI score, EASI-75 and IGA for completers and non-completers/early discontinued subjects. If rescue medication is taken before week 54 then data after the rescue medication should not be used for descriptive tables of week 54.

8.9. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and an IGA reduction from baseline of ≥2 points through Week 54 – Binary variable
- Proportion of subjects with EASI-75(≥75% improvement from baseline) through Week 54 – Binary variable
- Proportion of subjects who achieve an EASI-50 (≥50% improvement from baseline) through Week 54 – Binary variable
- Change in the EQ-5D through Week 16 – Continuous variable
- Change in Juniper ACQ-5 from baseline through Week 16 – Continuous variable
- Change in the SNOT-22 from baseline to Week 16 – Continuous variable
- To assess qualitative changes in photographs of skin lesions taken at time points specified in the Schedule of Assessment.

The analysis for the exploratory efficacy endpoint will be descriptive in nature and based on availability of the data as necessary.

8.10. Summary of Reasons for Efficacy Non-Evaluability / Exclusion from Efficacy Analyses

The reasons for excluding subjects from the FAS and PPS populations will be listed by treatment and subject.

9. PHARMACOKINETIC ANALYSES

PK analyses will be conducted based on PKAS for the blinded treatment phase.

An overview of blood sampling time points for the rich PK group and the sparse PK group is provided in Tables 2 in the protocol. Serum concentrations of ISB830 will be quantified using a validated ELISA method. The PK parameters derived using non-compartmental techniques will be regarded as primary endpoints for the PK analyses. Primary inference for all the PK parameters will be based on the PKAS population.

9.1. Presentation of PK Data, Descriptive Statistics and PK Assessment

PK serum concentration data will be listed by group (rich vs. sparse), treatment, subject, day and actual elapsed time point relative to first dosing and immediate dosing event for serum data. Serum concentrations will be summarized by treatment, day and nominal time point. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (%CV), geometric mean, median, minimum and maximum values, where $\%\mathrm{CV} = 100 \times \mathrm{SD}/\mathrm{mean}$.

Combined individual subject serum concentrations versus actual elapsed time points will be plotted by treatment and day, and also for the entire duration (spaghetti plots). Individual plots for each subject serum concentration vs actual elapsed time point for the entire duration will also be provided. Arithmetic and geometric mean plasma concentrations vs nominal times will

be presented in linear plots. All treatments will be overlaid on the same plot. Median trough ISB 830 concentrations vs nominal times will also be presented in linear plots.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to 5 significant digits);
- The mean, SD, geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of 4 significant digits;
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits;
- Coefficient of variation (%CV) and geometric coefficient of variation will be presented to 1 decimal place.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:

- Individual PK parameters will be presented to 4 significant digits, with the exception of t_{max}, which will be presented to 2 decimal places. In addition, parameters directly derived from source data (eg C_{max},) shall be reported with the same precision as the source data (if this is not 4 significant digits);
- The mean, geometric mean, median and SD values will be reported to 4 significant digits, all other descriptive statistics will be reported to 3 significant digits except for %CV and the geometric %CV, which will be presented to 1 decimal place. For t_{max} the minimum and maximum will be presented to 2 decimals places and the rest of the descriptive statistics to 3 decimal places;
- Estimates and CIs in the form of percentages will be presented to 2 decimal places.

Source data shall be used in all derived PK parameter calculations without prior rounding.

9.2. Pharmacokinetic Parameters

Derivation of PK parameters will be the responsibility of Early Phase, Quantitative Clinical Development (QCD), Parexel International and will be conducted either with Phoenix WinNonlin® Professional v.6.3 (or higher) or SAS® v.9.3 (or higher). The PK parameters for individual subject in Table 4: Pharmacokinetic Parameters

will be determined after dose administration.

Table 4: Pharmacokinetic Parameters

Parameter	Definition
After the First Dose for Group 1, 2, 3 and 5	
AUC_{0-t}	Area under the curve, from time '0' to time of last measurable concentration, using rich PK data set

$AUC_{0\text{-}tau}$	Area under the curve over the dosing interval, using rich PK data set
C_{max}	Maximum observed plasma concentrations during the dosing interval, using rich PK data set
t_{max}	Time at which C_{max} is observed, using rich PK data set
After the Dose on Week 12 for Group 1, 2, 3 and 5	
$AUC_{0\text{-}tauSS}$	Area under the curve over the dosing interval at steady state
$AUC_{0\text{-}tauSS}$/Dose	Dose-normalized area under the curve over the dosing interval at steady state
C_{avSS}	Average concentration during a dosing interval at steady state
C_{maxSS}	Maximum observed concentrations during the dosing interval at steady state
C_{maxSS}/Dose	Dose-normalized maximum observed concentration during the dosing interval at steady state
C_{minSS}	Minimum observed trough concentrations during the dosing interval at steady state
$t_{max,ss}$	Time at which C_{max} is observed at steady state
R_{ac}	Accumulation ratio for C_{max} and $AUC_{0\text{-}tau}$
PTF	Peak trough fluctuation
C_{trough}	Serum concentrations at end of dosing interval, using both rich PK and sparse PK data sets. In addition to after doses on Week 12 (Group 1, 2, 3 and 5) and Week 14 (Group 1 and 5 only), C_{trough} will be provided after Weeks 2, 4, 6, 8, 10, 12 dosing for Group 1 and Group 5, and after Weeks 4 and 8 dosing for Group 2 and Group 3, using both rich PK and sparse PK data sets

PK parameters will be calculated by non-compartmental analysis methods from the concentration-time data following these guidelines:

- Actual sampling times relative to immediate dosing rather than nominal times will be used in the calculation of all derived PK parameters;
- There will be no imputation of missing data;
- Any subjects with missing concentration data will be included in the PK analysis set. A decision will be taken on a case by case basis by the PK Scientist after consultation with the sponsor;
- C_{max} and C_{trough} will be obtained directly from the concentration-time data;
- t_{max} is the time at which C_{max} is observed;
- λ_Z will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression
    - A minimum number of three data points in the terminal phase will be used in calculation λz with the line of regression starting at any post -C_{max} data point (C_{max}

should not be part of the regression slope). The adjusted correlation coefficient (R^2 adjusted) in general should be equal to or greater than 0.80.

- The interval used to determine λz should be equal or greater than 1.5-fold the estimated half-life or otherwise flagged and used at the PK scientist's best knowledge and judgment. The corresponding estimated $t_{1/2}$ will need to be flagged or excluded from statistical analysis accordingly. The interval used to determine λz would be evaluated visually to confirm the appropriateness of the duration and will be selected manually if needed to.

- $t_{1/2}$ will be calculated as $\ln 2/\lambda_Z$
- AUC is calculated as follows:
  - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
  - $AUC_{0\text{-}t}=\int_0^t C(t)dt$.
  - $AUC_{0\text{-}tau}$ will be calculated using from time beginning to end of dosing interval using the linear up/log down method;
- $C_{max,ss}$ at steady state will be obtained directly from the concentration-time data.
- $C_{min,ss}$ at steady state will be obtained directly from the concentration-time data.
- $t_{max,ss}$ time at which $C_{max,ss}$ occurs at steady state.
- $AUC_{0\text{-}tau,ss}$: Area under the concentration-time curve over the dosing interval will be calculated using linear trapezoidal method; all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.
- $C_{av,ss}$: Average steady-state concentration calculated as $AUC_{(0\ \tau),ss/\tau}$.

The following PK parameters will also be derived.

- PTF: Peak trough fluctuation calculated as $(C_{max,ss} - C_{min,ss})/ C_{av,ss}$.
- R_{ac} : Accumulation ratio calculated as:
  - C_{max} (last dose interval)/ C_{max} (first dose interval)
  - $AUC_{(0\text{-}\tau),ss}$ (last dose interval)/ $AUC_{(0\text{-}\tau),ss}$ (first dose interval)
- $AUC_{0\text{-}tauSS}$/Dose
- C_{maxSS}/Dose

Serum PK parameters will be listed by group (rich vs sparse), treatment, subject and day, and summarized by treatment and day. Descriptive statistics for calculated PK parameters will include n, arithmetic mean, SD, %CV, geometric mean, geometric CV% (calculated as: geometric CV% =SQRT(es^2-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values. For t_{max} only median, minimum and

maximum values will be presented. No descriptive statistics will be determined when fewer than 3 individual PK parameters are available.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:

- Individual PK parameters will be presented to 4 significant digits, with the exception of t_{max}, which will be presented to 2 decimal places. In addition, parameters directly derived from source data (eg, C_{max},) shall be reported with the same precision as the source data (if this is not 4 significant digits);
- The mean, geometric mean, median and SD values will be reported to 4 significant digits, all other descriptive statistics will be reported to 3 significant digits except for %CV and the geometric %CV, which will be presented to 1 decimal place. For t_{max} the minimum and maximum will be presented to 2 decimals places and the rest of the descriptive statistics to 3 decimal places;
- Estimates and CIs in the form of percentages will be presented to 2 decimal places.

Source data shall be used in all derived PK parameter calculations without prior rounding.

9.3. Handling of Values Below the Limit of Quantification

All serum concentrations below the lower limit of quantification (LLOQ) or missing data will be labeled as below the limit of quantification (BLQ) or missing, respectively, in the concentration data listings.

BLQ values for the generation of serum PK parameters and for plotting of individual serum PK concentration data will be imputed in the PK concentration dataset used for the derivation of PK parameters. The following rules will be applied:

- BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration on the first day of dosing) will be assigned to zero;
- BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration on last day of dosing) will be set to missing;
- Single or consecutive BLQs which fall between measurable concentrations will be set to missing.
- Quantifiable concentrations falling between 2 BLQ values might be set to missing if considered anomalous by the pharmacokineticist after consultation with the Sponsor.

For linear plots, zero concentration value(s) will be included in the plot while missing values will be ignored. For log-linear plots, zero concentration value(s) will be assigned a ½ LLOQ value with the exception of the predose sample collected on Day 1 while missing concentrations at the end of the profile will be ignored.

BLQ values for summarizing serum PK concentration data will be imputed for mean concentration-time plots and tabular summaries according to the following rules:

- All BLQ values will be set to zero, except when an individual BLQ falls between two measurable values or 1 or more BLQs fall at the end of a subject profile, in which case they will be set to missing;
- Mean values will be reported only if calculated on a minimum of 3 quantifiable concentrations. The number of subjects contributing to the calculation of the mean will be specified in a footnote to the mean plots (both in linear and semi-log scales) if lower than the total amount of samples available per time point;

A high proportion of BLQ values may affect derivation of SD; if more than 30% of values at a time-point are imputed, then SD will not be displayed.

Tabular summaries for concentration-time data will report N (number of subjects who received treatment), n (number of subjects with non-missing values) and, if applicable, number imputed (number of subjects with imputed values (i.e., BLQ assigned zero concentration).

10. SAFETY AND TOLERABILITY

10.1. Overall Summary of Tolerability

The safety analyses will be based on the SAS. Safety will be assessed by evaluating AEs, SAEs, treatment related AEs and SAEs, anaphylactic events, injection site reactions, vital signs, physical examinations, ECG values, and laboratory test results.

10.1.1. Pandemic Related Safety Assessments

To ensure the ongoing safety of subjects during the pandemic, study subjects who miss or are unable to attend scheduled clinic visits will be contacted by the site via a safety phone call that includes the collection of AEs/SAEs and concomitant medications. This phone call is to be performed for every missed visit that occurs during the pandemic. If the subject meets other criteria, eg, for withdrawal/discontinuation of the study drug, the site is to follow the protocol in regard to those criteria. Subject withdrawal/discontinuation criteria are outlined in protocol Section 8.3.

10.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

10.2.1. Summaries of Adverse Event for All Subjects

- For each AE, the following information is to be recorded; the start date, the stop date (or whether the AE is ongoing at study completion/discontinuation), the severity and the investigational relationship of the AE to study drug, the therapy for the AE, the action taken with study drug, and whether or not the AE is considered serious.
- Adverse events will be coded by SOC and PT using the most recent version of MedDRA available in EDC at the time of analysis.
- TEAEs are defined as AEs (identified by PT) that begin or that worsen in severity after at least 1 dose of study treatment has been administered.

- The number and percentage of subjects reporting at least 1 occurrence of an AE and an AE leading to permanent discontinuation of study drug will be tabulated for each unique SOC and PT by severity, and by the relationship to study drug.
- For multiple occurrences of the same TEAE with the different severities, the TEAE with the highest severity will be tabulated. For multiple occurrences of the same TEAE with different relationships to study drug (related and not related), the TEAE will be tabulated as related.
- All TEAEs leading to permanent discontinuation of study drug will also be tabulated.
- All AEs for all subjects will be presented in a data listing.
- Physical examination baseline conditions that worsened post-baseline will be recorded on the AE form.
- All SAEs that occur after administration of the first dose of study drug will be listed by SOC, PT, and relationship to study drug.
- In addition to AE subtotals for each of the treatment groups, a total will be presented for all ISB 830 groups in the AE/SAE-related summary tables.
- The severity of AEs is classified (Table 5) according to the CTCAE v4.03 that was published 14-Jun-2010 by the US Department of Health and Human Services (National Institutes of Health [NIH] and National Cancer Institute [NCI]).

Table 5: Classification of Severity of Adverse Events (CTCAE v4.03)

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 activities of daily living[1] (ADL).
Grade 3	Severe	severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
Grade 4	Life-threatening	urgent intervention indicated.
Grade 5	Death	death related to AE.

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

[1]**Error! Reference source not found.** Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[2] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: CTCAE v4.03, 2010

The relationship of AEs to study drug is classified as follows:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility

- Related: A causal relationship between the study treatment and the AE is a reasonable possibility

10.2.2. Missing and Partial Adverse Event Onset Dates

Refer to Section 6.8.3.

10.2.3. Summaries of Serious Adverse Events, Adverse Event Dropouts and Death

For SAEs that are considered to be related to study drug, the number and percentage of subjects reporting at least 1 occurrence of an SAE for each unique SOC and PT will be tabulated. Any deaths will also be tabulated.

All AEs and SAEs will be presented for individual subjects in data listings, as well as premature discontinuations due to all causality. Deaths of all causes, study-drug related or not, will be presented in a separate listing. Pandemic related Impact of COVID-19 will be presented in listing (SAP Section 7.8).

10.2.4. Immunogenicity Analyses

The immunogenicity (IM) analyses will be based on the FAS, unless otherwise specified. Blood sample (5 mL each) will be collected at appropriate time points defined in Tables 2 and Table 3 in the protocol, to detect the presence of ADA to ISB830. Antibodies generated against ISB830 will be detected and confirmed using a validated Electrochemiluminescence immunoassay (ECLIA) method.

The objectives include the following:

- To evaluate sample IM status [confirmed positive/negative or unevaluable and, when applicable, titer of ADA] during treatment or placebo in all evaluable subjects
- To evaluate confirmed positive ADA subjects for neutralizing antibody status
- To evaluate potential relationships of IM with key efficacy, safety, and pharmacokinetic measures
- Definitions for subject IM results below are provided as a reference:
    1. Positive ADA response: Total of Treatment-Emergent and Treatment-boosted ADA in a cohort
    2. Positive Nab response: At least one post baseline measurement classified as neutralizing positive
    3. Treatment-Emergent ADA: Treatment-Emergent ADA incidence refers to percentage of the total number of evaluable subjects that were ADA-negative at baseline but developed antibodies following biologic drug administration.
    4. Treatment boosted ADA: Percentage of the total number of evaluable subjects that were ADA positive at baseline with at least fourfold increase in ADA titer after biologic drug administration are considered for computing treatment boosted ADA incidence.

5. Persistent ADA: Treatment-Emergent positive ADA detected at 2 or more consecutive sampling time points during the treatment or follow up period, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also, ADA detected only in the last sampling time point of the study.
6. Transient ADA: Any positive ADA response not considered persistent. Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.
7. ADA-positive subject: A subject with at least one treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment or follow-up observation period.
8. ADA-negative subject: A subject without a treatment induced or treatment-boosted ADA-positive sample during the treatment or follow-up observation period. A subject who tested ADA positive result in only the predose sample with ADA negative result in the time points following drug administration.
9. ADA-inconclusive subject: A subject who cannot clearly be classified as ADA-negative. A subject tested ADA negative at all-time points post drug administration with circulating drug concentration greater than the drug tolerance of the immunogenicity assay will be flagged and will not be considered for computation of overall ADA.
10. Evaluable subject: A subject with at least 1 sample taken after drug administration during the treatment or follow-up observation period that is appropriate for ADA testing (with reportable result). Only evaluable subjects are considered for computing treatment-induced ADA incidence.
11. Non-evaluable subject: A subject without a single sample taken (or without a reportable result) after drug administration during the treatment or follow-up observation period. However, whereas such a subject is excluded from treatment-emergent immunogenicity analyses, this subject ought to be included in the reporting of pre-existing ADA if the baseline sample had a reportable result.

Sample IM results (confirmed positive/negative or unevaluable) during treatment with study drug (treatment or placebo) will be listed by treatment, time point and dose.

Subject IM results will be listed by treatment and dose for all evaluable patients, which will include but may not be limited to: subject IM status (positive, negative or unknown), the study day associated with the first positive IM status (T_{first}, i.e., onset of ADA development) and the last positive IM status observed (T_{last}).

The overall treatment and post-treatment evaluation period, as well as subject IM incidence and incidence rate, will be determined and appropriately summarized by treatment, as the total number of and percentage of evaluated subjects with IM negative, positive, and unknown status. Furthermore, onset, titer overtime, and peak titer of the ADA response, if applicable, will be

also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range and presented graphically (eg, summarized at each evaluated study time point and overall; summarized by observed peak titer values from the individual IM positive subjects).

$\text{Overall \% incidence of ADA in a cohort} = \frac{(\text{Number of Subjects with treatment emergent ADA + treatment boosted ADA}) * 100}{\text{Total number of evaluable subjects in a cohort}}$
$\text{\% incidence of treatment emergent ADA in a cohort} = \frac{(\text{Number of Subjects with treatment emergent ADA}) * 100}{\text{Total number of evaluable subjects in a cohort}}$
$\text{\% incidence of treatment boosted ADA in a cohort} = \frac{(\text{Number of Subjects with treatment boosted ADA}) * 100}{\text{Total number of evaluable subjects in a cohort}}$

PK endpoints (C_{max} and $AUC_{0\text{-}tau}$) will be stratified by IM status of subject (i.e., IM positive, negative, unknown) from the rich PK group and C_{trough} values will also be stratified by IM status using data from both rich and sparse PK groups.

In addition to PK assessments, key efficacy and safety assessments may also be further stratified by IM status of subjects and presented in tables and/or graphically.

10.3. Treatment Compliance

The study drug compliance will be evaluated according to volume of injections during treatment period: [total volume injected during exposure period /total volume planned study drug injections during exposure period] × 100. Subjects with a compliance rate between 80% and 100% are considered as compliant with study drug during their participation in the study. Proportion of subjects considered as compliant with study drug will be summarized.

10.4. Concomitant and Other Medications

Concomitant medications and rescuer medications (such as TCS, TCI, crisaborole or phototherapy) will be coded using the most recent version of WHODD available in EDC at the time of analysis. Medication will be summarized by ATC level 2, level 3, and preferred name in frequency tables.

All concomitant medications taken since screening until the end of the study will be listed by treatment and subject.

10.5. Laboratory Data

Baseline and post-baseline clinical laboratory data (hematology, biochemistry, and urinalysis) will be obtained at the visits designated on the protocol Schedule of Assessments (Table 2 in the protocol).

Descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) will be presented for laboratory data as well as change from baseline by treatment and visit. In addition, values outside the respective normal range will be listed.

Anaphylactic events will be assessed by the Investigator based on guidance given in the protocol; Injection site reactions will be assessed according to the CTCAE v4.03. The number

and percentage of subjects reporting at least one occurrence of anaphylactic event will be summarized.

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point.

The number of subjects with values normal range and outside the respective normal range will be tabulated by treatment group. Shift in laboratory test relative to normal ranges from baseline will also be tabulated. Line Plots and bar charts will be presented.

All laboratory data will be listed by treatment and subject.

If any laboratory value falls above or below the upper or lower level of quantification, the value of the upper or lower level of quantification will be taken (e.g. <0.2 will become 0.2) for summaries but left as recorded in the listing.

10.6. Vital Signs

Vital sign measurements (i.e., systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiratory rate [breaths per minute], oral or tympanic temperature [degrees in Celsius]) will be obtained at the visits designated on the protocol Schedule of Assessments (Table 2 in the protocol) by standard methods. Blood pressure and pulse rate will be measured after the subject has been supine for 5 minutes. Height [cm], weight [kg] and BMI (kg/m^2) will also be recorded at Screening Visit.

Descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) will be used to summarize vital sign results and changes from baseline by treatment group and time. All vital sign data will be displayed in listings.

Shift tables will present changes from baseline (categorized as normal; abnormal) to end-of-treatment. The shift tables will be done only for SBP and DBP. The groups for SBP will be Normal < 140, Abnormal ≥140 and DBP will be Normal < 90, Abnormal ≥90.

All vital sign data will be listed by treatment and subject.

10.7. Electrocardiogram

Baseline and post-baseline electrocardiograms (12-lead ECG) will be obtained at the visits designated on the protocol Schedule of Assessments (Table 2 in the protocol). Subjects must be in a supine or recumbent position for a period of 5 minutes prior to the ECG.

The parameters to be reported are heart rate, RR interval (RR), PR Interval, QRS duration, QT interval, and corrected QT (QTc) interval (QTcF and QTcB). The absolute values and the change from baseline for ECG parameters will be summarized. An outlier analysis of ECG results will be conducted. All ECG variables will be presented by visit.

Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal) to end-of-treatment.

All ECG data will be listed by treatment and subject.

10.8. Physical Examination

Baseline and post-baseline physical examinations will be performed at the visits designated on the protocol Schedule of Assessments (Table 2 in the protocol). A comprehensive physical examination will include HEENT, cardiovascular system, respiratory system, musculoskeletal system, skin (non-atopic dermatitis related), gastrointestinal system, genitourinary system, and brief neurological examination. Urogenital and anorectal exams are optional. Sign/symptom-directed examination might be performed as per the Investigator's discretion.

Descriptive statistics (frequency and percentage) will be used to summarize physical examination results by body system, treatment group and visit.

All physical examination data will be listed by treatment and subject.

11. REFERENCES

1. Roderick J. A. Little, Donald B. Rubin - Statistical Analysis with Missing Data, 3rd Ed.- John Wiley & Sons (2019).

12. APPENDICES

The details on data display specifications and shells for Tables, Listings and Figures (TLFs) are presented in separate document titled 'Table, Listing, Figure (TLF Shell)'.