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 During the screening period, treatments for AD will be withdrawn or modified for the subject as defined in the protocol (Table 5).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.

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

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).

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]

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

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.

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

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

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.

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

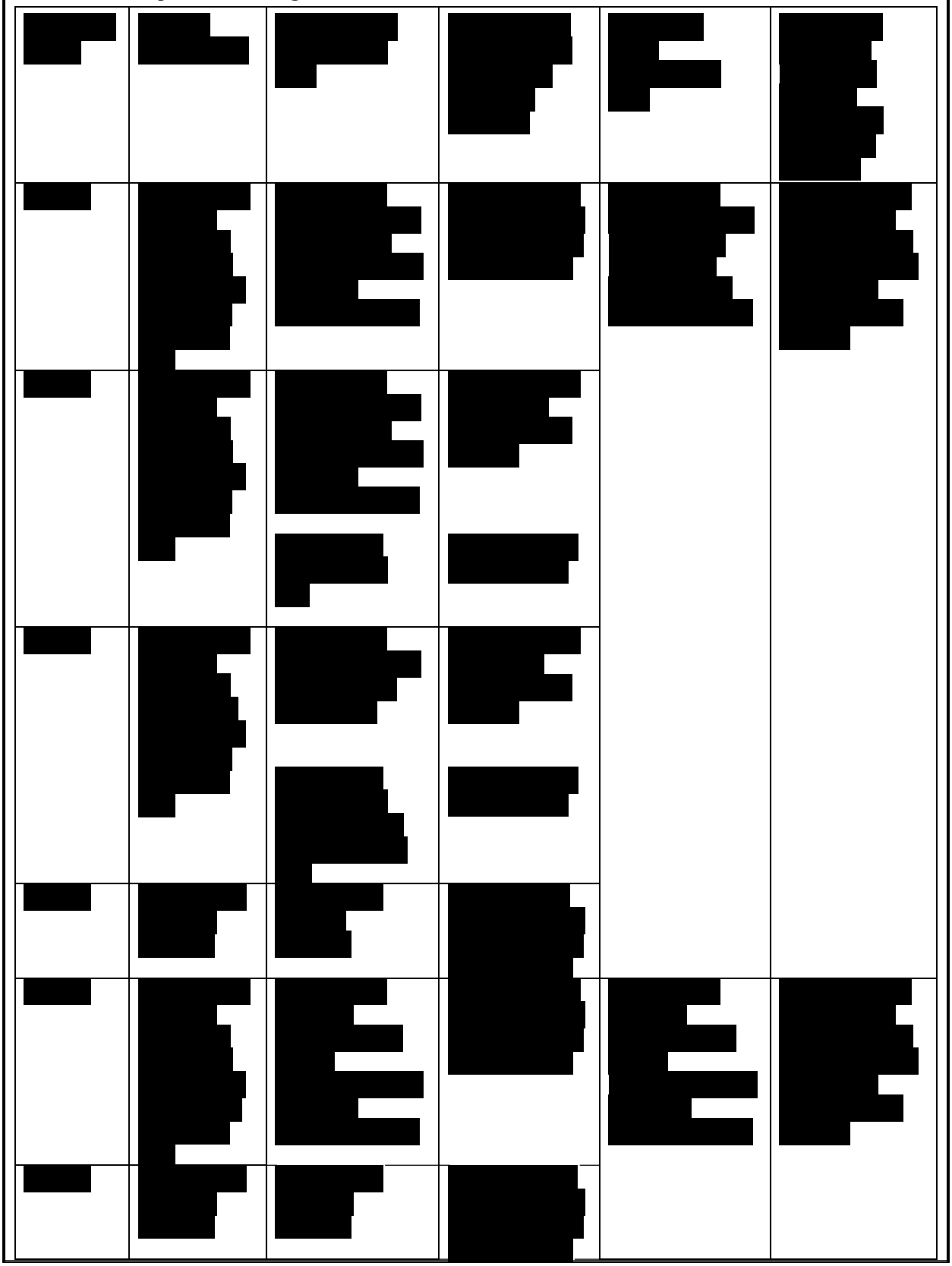
Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- 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.

Treatment Groups and Dose Regimens



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

- 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

Table 6: Treatment Groups and Dose Regimens

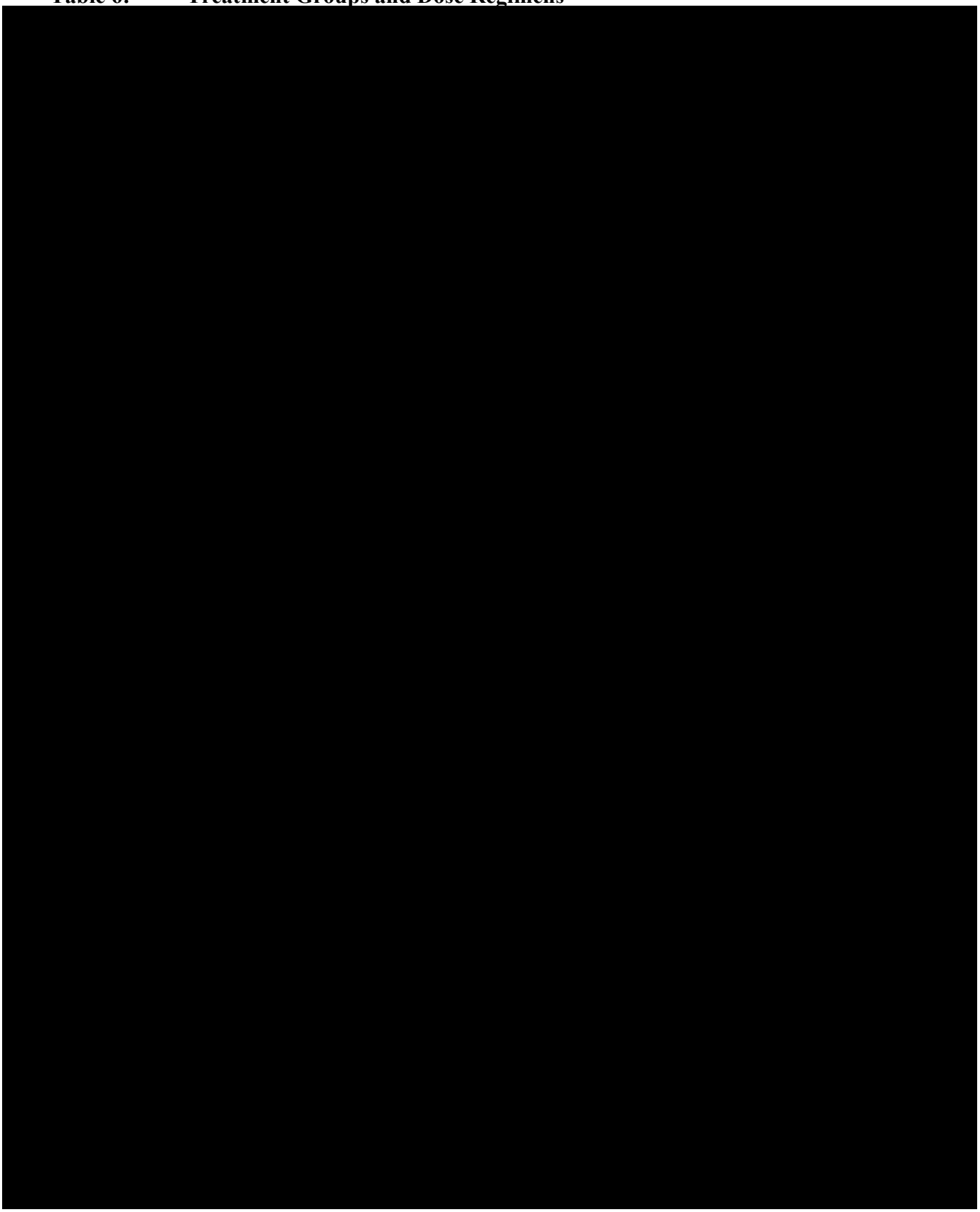


Table 8: Pharmacodynamic (Biomarker), Pharmacokinetic, and Immunogenicity Blood Sampling Time Points (Continued)

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

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]).

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

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],

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.

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