Statistical Analysis Plan

A Phase 1b/2a Study to Evaluate the Safety, Pharmacokinetics and Efficacy of IMG-007 in Adult Participants with Moderate-to-Severe Atopic Dermatitis

Investigational Product:	IMG-007
Protocol Number:	IMG-007-201
Statistical Analysis Plan Version:	Version 1.1
Version Release Date:	17 May 2024
Sponsor:	Inmagene LLC

Signature Page

Declaration

The undersigned have reviewed and agreed to the statistical analysis and procedures of this clinical study, as presented in this document.

Statistical Analysis Plan Version: 2.0

Statistical Analysis Plan Date: 17 May 2024

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Inmagene Biopharmaceuticals

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Version History

SAP Version	**Date**	**Change**	**Rationale**
1.0	26Feb2024	Not applicable	First version
2.0	17May2024	Cohort 2 is removed from the analysis	The screening and enrolment to the placebo-controlled cohort 2 is terminated.

List of Abbreviations

AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
CL	Central Compartment Clearance
CRO	Contract Research Organization
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI-50	≥ 50% reduction from baseline in EASI
EASI-75	≥ 75% reduction from baseline in EASI
EASI-90	≥ 90% reduction from baseline in EASI
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOI	End of Infusion
EOS	End of Study
EOT	End of Treatment
HBcAb	Antibody to Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
IV	Intravenous
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
NRS	Numerical Rating Scale
OX40L	OX40 Ligand
PD	Pharmacodynamic

PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PT	Preferred Term
RM	Rescue Medication
RO	Receptor Occupancy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SQ-NRS	Sleep Quality Numerical Rating Scale
SRC	Safety Review Committee
TARC	Thymus- and Activation-regulated Chemokine
TB	Tuberculosis
TCI	Topical Calcineurin Inhibitors
TCS	Topical corticosteroid
TEAE	Treatment Emergent Adverse Event
TNFR	Tumor Necrosis Factor Receptor
UV	Ultraviolet
Vc	Central Compartment Volume
VS	Vital Sign
WHODrug	World Health Organization Drug Dictionary
WI-NRS	Worst Itch Numerical Rating Scale

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying statistical approaches for the analysis of this study. The SAP is intended to be a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for IMG-007-201. This SAP was written and finalized prior to the database lock, based on study protocol IMG-007-201 Version 6.0 (05Feb2024). Any methodological deviations from the protocol are documented. The analyses laid out in this SAP will be implemented by MeDaStats LLC for Inmagene Biopharmaceuticals.

1.1 Background and Rationale

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by sensitive and dry skin, localized or disseminated eczematous lesions usually accompanied by a severe itching sensation. The etiologies of AD include epidermal barrier defects as well as dysregulation of both the innate and adaptive immune systems, which result in a series of inflammatory responses involving complex cytokines and chemokines (including T-helper [Th]2 and Th1 cytokines, interleukin [IL]-22 and IL-17).

Currently, topical agents such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) are the first-line pharmacological agents for the management of AD. Patients with moderate-to-severe AD who do not show adequate response to topical agents or develop side effects are candidates for systemic therapy. Despite availability of novel targeted systemic therapies such as mAbs against IL-4 and IL-13, there remains unmet needs in the long-term management of moderate-to-severe AD. Antagonists of OX40-OX40L signaling pathway represent promising potential therapeutics for the treatment of moderate-to-severe AD.

OX40 (CD134) is a member of the tumor necrosis factor receptor (TNFR) family and is expressed on both activated $CD4^+$and $CD8^+$T cells, neutrophils, and nature killer cells. Unlike other constitutive T-cell costimulatory receptors, OX40 is not expressed on naïve T cells. The OX40L is also a member of the TNFR superfamily and mainly expressed on activated antigen-presenting cells, such as dendritic cells, activated B cells, and macrophages. Recent studies have found that the costimulatory T-cell receptor OX40 and its ligand, are crucial for the generation of Th2 memory cells and may thus play a critical role in the pathogenesis and chronicity of AD. The expression of OX40 by activated skin homing $CD4^+$T cells is increased in patients with AD, and $OX40^+$ and $OX40L^+$ cells are co-located within the dermis, indicating local activity of OX40/OX40L. Several OX40 antagonists, such as telazorlimab (GBR 830) and rocatinlimab (KHK4083), have shown evidence of clinical effect in moderate-to-severe AD with durable efficacy after discontinuation of study treatment. OX40 antagonists may be a new approach to systemic AD therapy upon further development.

Compared with the other two OX40 antagonists with reserved (telazorlimab) or enhanced (rocatinlimab) antibody-dependent cellular cytotoxicity (ADCC) function, IMG-007 is developed with modifications in the Fc region to remove glycosylation intended to abolish ADCC, thereby minimizing potential toxicities associated with T cell depletion.

1.2 Study Objectives

1.2.1 Primary Objective

To evaluate adverse events (AEs) emergent from multiple doses of IMG-007 in adult participants with atopic dermatitis (AD)

1.2.2 Secondary Objectives

- To characterize the pharmacokinetic (PK) profile of multiple doses of IMG-007 in AD participants
- To evaluate the efficacy of multiple doses of IMG-007 in AD participants as measured by eczema area and severity index (EASI) at Week 12

1.2.3 Exploratory Objectives

- To evaluate the efficacy of multiple doses of IMG-007 in AD participants as measured by EASI, investigator's global assessment (IGA), scoring atopic dermatitis (SCORAD) index, patient-assessed itch and sleep quality numerical rating scale (SQ-NRS), patient global impression of severity (PGIS) of AD, patient global impression of change (PGIC) of AD, and dermatology life quality index (DLQI)
- To further characterize the safety and tolerability of multiple doses of IMG-007 in AD participants
- To evaluate the pharmacodynamic (PD) effect of IMG-007 on biomarkers in AD participants
- To evaluate the immunogenicity of IMG-007 in AD participants

2. INVESTIGATIONAL PLAN

2.1 Study Design and Randomization

IMG-007-201 is a phase 1b/2a study to assess the safety, tolerability, PK, efficacy, and PD of multiple doses of IMG-007 in participants with AD. The study will consist of three periods: a screening period of up to 5 weeks, a 12-week treatment period, and a 12-week follow-up period. Approximately 55 participants will be enrolled. The study will consist of two dose cohorts to be initiated sequentially in an ascending dose order: Cohort 1 will be open-label, with approximately 15 participants to receive three intravenous (IV) infusions of IMG-007 300 mg over 4 weeks; Cohort 2 will be randomized, double-blind and placebo-controlled, with approximately 40 participants to be randomized in a 3:1 ratio to receive three IV infusions of IMG-007 [redacted] or matching placebo over 4 weeks. Randomization will be stratified by disease severity (IGA 3 or IGA 4) at baseline. [redacted]

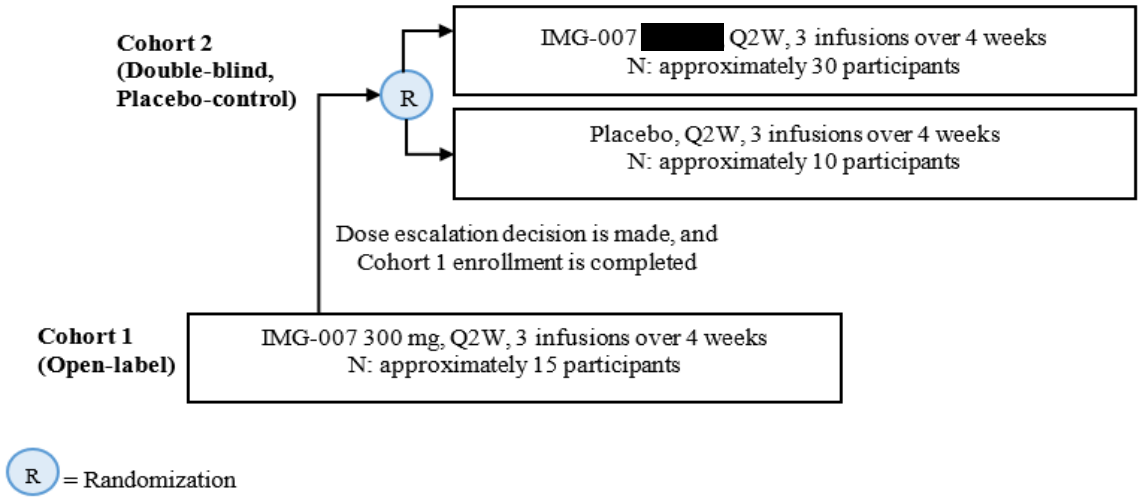

Figure 1 Study Schema

2.2 Sample Size Determination

The sample size of approximately 15 participants in Cohort 1 and approximately 40 participants in Cohort 2 is based on the study design for the initial characterization of the safety, PK and efficacy of IMG-007 in AD patients. For Cohort 2, the total sample size of approximately 40 participants will consist of approximately 30 participants receiving IMG-007 [redacted] and approximately 10 participants receiving matching placebo. The study is not powered to detect specific target treatment effect difference versus placebo but is based on feasibility considerations. [redacted]

2.3 Study Plan

The study consists of a screening period, a treatment period and a follow-up period.

Screening Period: Day -35 to Day -1 (up to 5 weeks)

After providing informed consent form (ICF), participants will be assessed for compliance with protocol requirements and study eligibility. Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g., delayed laboratory results), will a longer screening period be permitted for up to three business days. Upon consultation with the medical monitor, a participant may be rescreened one time. Circumstances that may permit rescreening include, but are not limited to, a laboratory test result that does not meet eligibility requirements. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Participants will be required to apply a stable dose of a non-medicated emollient (moisturizer) twice daily for at least one week prior to the Baseline visit.

Treatment Period: Day 1 (Baseline) to Day 85 (12 weeks)

Participants who are eligible and enrolled in Cohort 1 will receive three IV infusions of IMG-007 300 mg administered 2 weeks apart at Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) in an open-label fashion. Participants who are eligible and enrolled in Cohort 2 will be randomized (3:1) in a blinded fashion to receive three IV infusions of IMG-007 [redacted] or matching placebo 2 weeks apart at Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29).

On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes with a slower rate during the first 15 minutes.

Participants will complete additional visits at Week 1 (Day 8), Week 6 (Day 43), Week 8 (Day 57) and Week 12 (Day 85)/end of treatment (EOT).

Follow-up Period: Day 86 to Day 169 (12 weeks)

The follow-up period consists of three visits: Week 16 (Day 113), Week 20 (Day 141) and end of study (EOS; Week 24/Day 169) Visits.

3. ANALYSIS SETS

The following analysis sets will be used for all statistical analyses covered within the scope of this analysis plan. There could be other analysis sets outside the scope of this SAP for dedicated purposes, such as population PK analysis.

The analysis sets defined below are based on guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998).

3.1 Safety Analysis Set

Safety analysis set includes all participants from Cohorts 1 and 2 who received at least one dose of study treatment. Data will be analyzed by treatment group (i.e., 300 mg, [redacted] or placebo) based on the actual treatment received.

Safety analysis set will be used for safety analyses and also be used for demographic and baseline characteristics.

3.2 Modified Full Analysis Set

Modified full analysis set includes all participants from Cohorts 1 and 2 who received at least one dose of study treatment. Data will be analyzed by treatment group based on the treatment assigned or randomized.
Modified full analysis set will be used for all efficacy analyses.

3.3 Pharmacokinetic Analysis Set

PK analysis set includes all participants from Cohorts 1 and 2 in the safety analysis set who also received IMG-007 and have baseline and at least one post-baseline evaluable data point. Data will be analyzed by treatment group based on actual treatment received.

3.4 Immunogenicity Analysis Set

Immunogenicity analysis set includes all participants from Cohorts 1 and 2 in the safety analysis set who also have baseline and at least one post-baseline evaluable data point. Data will be analyzed by treatment group based on actual treatment received.

3.5 Pharmacodynamic Analysis Set

Pharmacodynamic (PD) analysis set includes all participants from Cohorts 1 and 2 in the safety analysis set who also have baseline and at least one post-baseline evaluable PD/biomarker data point. Data will be analyzed by treatment group based on the actual treatment received.

4. ANALYSIS VARIABLES

4.1 Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age, Sex, Ethnicity, Race, Height, Baseline weight, Baseline body mass index (BMI).
- Baseline AD Characteristics: Duration of AD, Atopic comorbidities, EASI, IGA (Moderate or Severe), AD involvement of body surface area (BSA), SCORAD, itch NRS, sleep quality NRS, PGIS, DLQI, and thymus and activation-regulated chemokine (TARC).

Duration of AD will be calculated as:

(Date of enrolment – Diagnosis date of AD)/365.25.

In cases where only a partial date is available for AD diagnosis, the imputation process will involve substituting "01" if only the day is absent, or "01 Jan" if both the day and month are missing, prior to the calculation of the duration.

4.2 Medical History and Atopic Disease History

Medical history will be coded according to the latest available version (26.0 or higher) of medical dictionary for regulatory activities (MedDRA) at the coding contract research organization (CRO). Information on conditions related to AD includes diagnosis of AD, AD history, applicable atopic/allergic diseases etc.

4.3 Prior and Concomitant Medications/Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit. Medications will be coded according to the latest available version (WHO Drug B3 Global, Sep 2022 or higher) of World Health Organization Drug Dictionary (WHODrug) at the coding CRO.

Prior medications/procedures: Medications taken or procedures performed prior to the first dose of Investigational Medicinal Product (IMP). All the medications that are stopped prior to the first administration of the study drug are considered under this category.

Concomitant medications/procedures: medications taken or procedures performed following the first dose of study drug through the EOS visit. i.e., procedures or medication with end date on or after the first administration of the study drug irrespective of the start date, or ongoing during the study period.

Prohibited medications and non-drug therapies:
Treatment with the following concomitant medication is prohibited from screening to study completion:

- Topical treatment including, but not limited to, TCS, TCI, topical phosphodiesterase-4 inhibitors, and topical janus kinase (JAK) inhibitors for AD within 2 weeks before the Baseline visit and until completion of the follow-up period. Current use of nasal or inhaled corticosteroids is allowed during the study.
- Non-biologic systemic (oral or injectable) agents including conventional immunosuppressants or immunomodulators (e.g., corticosteroids, methotrexate, cyclosporin, tacrolimus, mycophenolate mofetil, azathioprine, JAK inhibitors), and other approved drugs with potential immunosuppressive effects, within 4 weeks or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit and until completion of the follow-up period.
- Biologic therapy including approved and investigational agents (e.g., mAbs against IL-13 or IL-4 alpha, investigational mAbs against IL-31 or IL-31 receptor) within 3 months or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit and until the completion of the follow-up period.
- Treatment with a live (including live attenuated) vaccine within 2 months before the Baseline visit and until 3 months after the last administration.

The following concomitant procedures are prohibited during study participation:

- Phototherapy of AD with UVA or UVB or regular use of a tanning booth within 4 weeks of the Baseline visit and until the completion of the follow-up period.

Rescue therapy: If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment for AD may be prescribed to study participants at the discretion of the investigator. Any participant who requires topical corticosteroid (TCS) treatment may continue study treatment and should receive the TCS for as brief a period as possible. TCIs may be used for rescue, but should be reserved for problem areas only, e.g., face, neck, intertriginous and genital areas, etc. If a participant receives rescue treatment with a prohibited systemic medication, study treatment should be permanently discontinued.

If possible, investigators should attempt to limit the first step of rescue therapy to topical medications and escalate to systemic medications only for participants who do not respond adequately to at least 7 days of topical treatment. Where feasible, an unscheduled visit should

be performed to conduct all efficacy and safety assessments (as well as PK/PD sampling, if it is feasible) before administering any systemic rescue treatment.

4.4 Prior and concomitant non-drug therapies and procedures

Non-drug therapies will be recorded from the day of informed consent until the EOS visit and each therapy will be coded according to the latest available version (26.0 or higher) of MedDRA.

4.5 Efficacy Variables

Since the primary objective of the study is to assess the safety arising from multiple doses of IMG-007, the analysis of efficacy will be conducted as secondary and exploratory.

4.5.1 Secondary Efficacy Variable

The secondary efficacy endpoint is the percentage change in EASI from baseline to week 12.

Eczema Area and Severity Index (EASI)

The EASI is a validated composite scoring system assessed by the investigator based on the body area involved in each of the four body regions (head and neck, upper limbs, lower limbs, and trunk) and the average severity of each of the four key signs of AD (erythema, edema/papulation, excoriation, and lichenification) based on a 4-point scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), (Hanifin 2001). Symptoms (e.g., pruritus) and secondary signs (e.g., xerosis, scaling) are excluded from the assessment. The total EASI score ranges from 0 (clear or no eczema) to 72 (maximum severity), with the higher values indicating more severe and/or extensive disease. A score of 0 to 72 will be recorded. All assessments will be recorded in an appropriate electronic case report form (eCRF) according to the completion guidelines.

The EASI will be assessed by the investigator at selected scheduled and unscheduled clinic visits.

The EASI score will be computed at the dataset level, irrespective of its presence in the eCRF. However, the EASI score recorded in the eCRF will be utilized for the efficacy analysis. The derivation of EASI score is provided in the Appendix 12.3.

4.5.2 Exploratory Efficacy Variables

4.5.2.1 Key Exploratory Endpoints

The key exploratory endpoints are:

- Mean and mean % change from baseline in EASI by visit
- Proportion (%) of participants achieving EASI-50 by visit
- Proportion (%) of participants achieving EASI-75 by visit
- Proportion (%) of participants achieving EASI-90 by visit
- Mean change from baseline in IGA by visit
- Proportion (%) of participants achieving ≥ 1-point reduction from baseline in IGA by visit

- Proportion (%) of participants achieving ≥ 2-point reduction from baseline in IGA by visit
- Proportion (%) of participants achieving IGA 0 or 1 (clear or almost clear) and ≥ 2-point reduction from baseline by visit
- Mean and mean % change from baseline in SCORAD and Objective-SCORAD (O-SCORAD)by visit
- Mean and mean % change from baseline in worst itch numerical rating scale (WI-NRS) by visit
- Proportion (%) of participants achieving a ≥ 4-point reduction from baseline in WI-NRS by visit in participants with WI-NRS ≥ 4 at Baseline
- Mean and mean % change from baseline in sleep quality numerical rating scale (SQ-NRS) by visit

Investigator's Global Assessment (IGA)

The IGA is intended to assess the global severities of key acute clinical signs of AD, including erythema, induration/papulation, oozing/crusting (lichenification excluded) based on a 5-point scale of clear (0), almost clear (1), mild (2), moderate (3) and severe (4). A grade of 0 to 4 will be scored by the investigator. Assessments will be recorded in the eCRF.

The IGA will be performed by the investigator at selected scheduled clinic visits.

SCORing Atopic Dermatitis (SCORAD) and Objective-SCORAD (O-SCORAD)

The validated SCORAD index uses the rule of nines to assess disease extent and evaluates six clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3) oozing/crust, (4) excoriation, (5) lichenification, and (6) dryness (ETFAD 1993). The SCORAD index also assesses subjective symptoms of pruritus and sleep loss. These three domains (extent of disease, disease severity, and subjective symptoms) combine to give a maximum possible score of 103. The objective SCORAD consists of the extent and the intensity items, and the maximal possible O-SCORAD score is 83. Assessments will be recorded in the eCRF.
The SCORAD will be assessed at selected scheduled clinic visits.

The SCORAD and O-SCORAD will be computed at the dataset level, irrespective of its presence in the eCRF and the resulting calculated values will be utilized for the efficacy analysis. The SCORAD index will be calculated as specified in the Appendix 12.4.

Itch and Sleep Quality Numerical Rating Scale (NRS)

At scheduled and unscheduled clinic visits, participants will assess the worst intensity itch due to AD per an NRS (WI-NRS, where 0 = "none" and 10 = "worst imaginable") [redacted].

At scheduled clinic visits, participants will assess sleep quality per an NRS (SQ-NRS, where 0 = "best possible sleep" and 10 = "worst possible sleep") [redacted].

4.5.2.2 Other Exploratory Endpoints

Other exploratory efficacy endpoints are:

- Change from baseline in percent body surface area (BSA) by visit
- Change from baseline in PGIS by visit
- Proportion (%) of participants with PGIS of 0 or 1 by visit
- Proportion (%) of participants reporting PGIC of "much better" or "a little better" by visit
- Change from baseline in DLQI by visit
- Proportion (%) of participants achieving ≥ 4-point reduction from baseline in DLQI by visit in participants with DLQI ≥ 4 at baseline

Body Surface Area (BSA)

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the investigator using the rule of nines.
Participant will undergo this assessment at selected scheduled clinic visits.

Patient Global Impression of Severity (PGIS) of AD

At the scheduled clinical visits, participants will rate the severity of their AD over the past week on a 5-point scale ranging from 0 = "none" to 4 = "very severe".

Patient Global Impression of Change (PGIC) of AD

At the scheduled clinical visits, participants will rate the change in their AD on a 5-point scale ranging from 1 = "much better" to 5 = "much worse". Participants will be asked to provide this rating in comparison to just before the participant started taking study treatment.

Dermatology Life Quality Index (DLQI)

The DLQI is a validated 10-question instrument used to measure the impact of skin disease on the quality of life (QoL) of an affected person over the previous week. The ten questions cover the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and treatment (Finlay, Khan. 1992). The DLQI score ranges from 0 (no impact of skin disease on QoL) to 30 (maximum impact on QoL).

The DLQI is completed by the participant in the study clinic. Assessments will be recorded in the eCRF.

4.6 Safety Variables

4.6.1 Adverse Events and Serious Adverse Events Variables

Adverse events and serious adverse events will be collected from the time of informed consent signature until the end of the study. All adverse events will be coded according to the latest available version (26.0 or higher) of MedDRA.

An **Adverse Event** is the development of any untoward medical occurrence in a participant or clinical study participant who is administered with a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, including the following conditions:

1) Any newly occurred undesirable medical condition (including newly diagnosed disease or signs and symptoms when a diagnosis is pending);
2) Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. However, events that are unequivocally due to natural disease progression of the underlying disease being studied should not be reported as an AE during the study unless judged by the investigator to be more severe than expected for the participant condition;
3) Clinically significant laboratory abnormality.

A **Serious Adverse Event** is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- **Results in death**
- **Is immediately life threatening**
- **Requires in-patient hospitalization or prolongation of existing hospitalization**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital abnormality or birth defect**
- **Is an important medical event** (i.e., that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.)

Details for each criterion above are presented in the study protocol section 8.1.2.

Non-treatment emergent AEs (non-TEAEs) are AEs that are developed or worsened in severity compared to the baseline during the period between participant enrolment and study drug administration. all AEs collected during the screening period are considered as non-TEAEs.
Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment and follow-up period. As only the worsening pre-existing AEs and new AEs reported during the treatment and follow-up period will be collected in the study, all AEs collected during the treatment and follow-up period are considered as TEAEs.

TEAE that are infusion related reaction will be summarized. These TEAEs are localized injection/infusion reactions that may include pruritus, pain, erythema, swelling, rashes, or bleeding around the injection/infusion site. Systemic injection/infusion-related reactions may be immediate type or delayed type immune complex-associated hypersensitivity reactions (e.g., serum sickness).

4.6.2 Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be drawn at the timepoints as described in the Schedule of assessment (SoA) (Appendix 12.1) and analyzed at central laboratories.

Hematology	**Serum chemistry**[a]	**Urinalysis**[b]
Red blood cell count Hemoglobin Reticulocyte % White blood cell count Neutrophils % Neutrophils Lymphocytes % Lymphocytes Monocytes % Monocytes Eosinophils % Eosinophils Basophils % Basophils Platelets	Total protein Albumin Alkaline phosphatase Total bilirubin Aspartate aminotransferase Alanine aminotransferase Lactate dehydrogenase Sodium Potassium Chloride Urea/ blood urea nitrogen Creatinine Calcium Phosphate Uric acid Glucose	pH Glucose Protein Blood Ketones Nitrite Leukocyte Urobilinogen Bilirubin Specific gravity
Other tests		
HBsAg HBsAb HBcAb HCV antibody HIV antibody QuantiFERON-TB Gold or an equivalent test Pregnancy test (women of childbearing potential only)[c] Serum tryptase[d]		

a) Fasting is recommended but not mandatory. The status of fasting or non-fasting should be recorded in the study source document.

b) If any abnormalities are found in urinalysis, then microscopy should be conducted to examine red cells, white cells, bacteria, casts, and crystals.

c) Serum human chorionic gonadotropin (hCG) will be performed at the Screening, Baseline (Day 1), Week 2 (Day 15), Week 4 (Day 29) visits, and at selected follow-up visits. In addition, urine pregnancy test must be performed prior to dosing at Baseline (Day 1), Week 2 (Day 15) and Week 4 (Day 29).

d) For diagnostic purposes, any participant who experiences any systemic infusion-related event should have a blood sample taken ideally 30-60 minutes after the onset for tryptase testing, and samples may be analyzed by a central or local laboratory.

4.6.3 Vital Signs and Physical Examination Variables

The following vital signs (VS) parameters will be collected:

- Weight (kg) and height (cm)
- Systolic and diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Temperature (C)
- Respiratory rate (breaths/min)

Weight and height will be measured only at baseline. Other vital signs parameters will be collected as specified in the SoA (Appendix 12.1). On study treatment dosing days, i.e., Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29), vital signs should be assessed before initiation of infusion; 15 (± 5) minutes after the initiation of the infusion; 15 (± 5) minutes after end of infusion (EOI), and 1 hour (± 15 minutes) post EOI.

A complete physical examination will include, at a minimum, assessments of the skin, head and neck, cardiovascular, respiratory, gastrointestinal, and neurological systems and the assessment will be performed as specified in the SoA (Appendix 12.1).

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Symptom-directed physical examinations will be completed at each follow-up visit at the discretion of the investigator.

Investigators will be instructed to pay special attention to clinical signs related to previous serious illnesses. Unscheduled physical examinations can be conducted at the discretion of the PI or designee.

4.6.4 12-Lead Electrocardiogram (ECG) Variables

The following ECG parameters will be collected along with their corresponding clinical significance:

- Heart rate (bpm)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- QTcB interval (msec)
- QTcF interval (msec)

Triplicate ECG will be taken if there are any clinically significant abnormalities detected by the physician in a single ECG. The ECG assessment will be performed at timepoints listed in the SoA (Appendix 12.1).

4.7 Pharmacokinetic (PK) Variables

The blood samples will be collected at day 1/baseline (pre-dose and EOI), days 8, 15 (pre-dose and EOI), 29 (pre-dose and EOI), 43, 57, 85/EOT, 113, 141, and 169/EOS to describe IMG-007 concentration profiles at specified visit.

4.8 Immunogenicity Variable

The variables include anti-drug antibody (ADA) status (positive or negative) as follows:

- Total participants negative in the ADA assay at all time points analyzed
- Total participants positive in the ADA assay at any time point analyzed
- Total participants with pre-existing ADA
- Total participants with treatment emergent response
- Total participants with treatment boosted response

- *Pre-existing ADA*: Either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels.
- *Treatment-boosted response*: Pre-existing ADA that is increased to a higher concentration (4-fold or higher level) after administration of therapeutic protein product.
- *Treatment-emergent response*: ADA developed de novo (seroconversion) following administration of therapeutic protein product in a participant who lacked detectable pre-existing ADA

    a. *Persistent response*: Treatment-emergent response detected at 2 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 of 16 weeks or longer.
    b. *Indeterminate response*: as a treatment-emergent response with only the last collected sample positive in the ADA assay
    c. *Transient response:* Treatment-emergent response detected only at 1 sampling time point during the treatment or follow-up observation period, or 2 or more time points during the treatment, where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the participant's last sampling timepoint is ADA-negative.

Blood sample for the immunogenicity analysis will be collected at Day 1/Baseline (pre-dose), days 15(pre-dose), 29 (pre-dose), 43, 57, 85/EOT, 113, 141, and 169/EOS.

5. CHANGES TO PLANNED ANALYSIS FROM PROTOCOL

Screening and enrollment for the placebo-controlled cohort 2 of the study were terminated by sponsor following the communication letter titled 'Enrollment Communication' dated 18Mar2024. Consequently, the study now comprises only one treatment group (IMG 300 mg). Henceforth, all analyses and result reporting will involve only one treatment group. Analyses related to the placebo-controlled cohort (i.e., cohort 2) are no longer applicable and this will not be reported.

6. STATISTICAL METHODS

For continuous variables, at the reported visits or in overall summary, descriptive statistics will consist of number of participants with observations (n), mean, median, standard deviation (SD),

minimum, and maximum. It is noted that number of participants with observations could include participants with data that were observed as well as those that were imputed for specific types of missing data or determined based on handling of intercurrent events, as explained in later sections.

For categorical variables, frequencies and percentages will be displayed for each category.

In the context of efficacy-related tables, percentages will be calculated based on the denominator of number of participants with data depending on the handling of intercurrent events as well as imputations of missing data as explained in the later sections. For non-efficacy tables, percentages will be calculated based on the corresponding analysis population unless otherwise specified in the mock shell.

Listed below are some subgroups for potential exploratory subgroup analysis:

- Race (Black/African American vs. Non-Black/Non-African American)
- Age group (18-64 years old vs. ≥65 years old)
- EASI Score at baseline (EASI<=21 (moderate) and EASI>21 (severe))
- Disease severity based on IGA score (moderate, defined as IGA at baseline =3 vs. severe, defined as IGA at baseline =4)
- Baseline TARC [redacted]
- Age at disease onset (≤12 years old vs. >12 years old)
- Presence of atopic comorbidities (Yes vs. No)
- History of biologics/JAK-I failure

6.1 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized based on safety analysis set. Listing of demographics and baseline characteristics will be presented.

6.2 Medical and AD History

Non-atopic medical history and comorbid (concomitant) non-atopic medical illness will be summarized by primary system organ class (SOC) and preferred term (PT). Atopic disease history and comorbid (concomitant) atopic medical illness will be summarized separately in the safety analysis set by type of disease. The table will be sorted by decreasing frequency of SOC followed by PT (or disease type in case of atopic disease history).

Medical history will be listed by SOC and PT, based on the safety analysis set.

6.3 Prior and Concomitant Medications/Procedures for AD

Below summaries will be provided on prior and concomitant medications/procedures for treatment of AD for the safety analysis set, sorted by decreasing frequency of anatomic therapeutic class (ATC) level 2 (pharmacological or therapeutic subgroup) and preferred term.

- Summary of prior medications related to AD by ATC level 2 and preferred term.
- Summary of prior medications related to AD by type of medication

- Summary of prior medications related to AD by reason for discontinuation, ATC level 2 and preferred term
- Summary of prior medications related to AD by reason for discontinuation and type of medication.
- Summary of concomitant medications related to AD by ATC level 2 and preferred term.
- Summary of rescue medication (RM) by ATC level 2 and preferred term
- Summary of the duration of RM by ATC level 2 and preferred term

The duration of RM will be calculated as:

(Date of last usage of RM – Date of first usage of RM) + 1

If a participant has utilized RM on multiple occasions, the total duration will be calculated as the cumulative sum of each RM duration. A summary of the duration of rescue medications by type of medication will be presented.

Listings will be provided for prior and concomitant medications/procedures for AD and rescue medication for the safety analysis set. The listings will include ATC level 2 and preferred terms, indication, dose, frequency, route, start date, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day).

6.4 Prior and Concomitant Medications for non-AD

Below summaries will be provided on prior and concomitant medications/procedures for non-AD conditions for the safety analysis set, sorted by decreasing frequency of ATC level 2 and preferred term.

- Summary of prior non-AD medications by ATC level 2 and preferred term.
- Summary of concomitant non-AD medications by (ATC level 2 and preferred term.

Listings will be provided for non-AD medications (prior and concomitant) for the safety analysis set. The listings will include reported term, ATC level 2, Indication, dose, frequency, route, start date, study day onset (for medications started before treatment, the study day onset (defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset = date of medication start - date of the first dose+1), end date and end study day (defined similarly as for study onset day).

6.5 Prior and Concomitant non-Drug Therapies and Procedures

Below summaries will be provided on prior and concomitant non-drug therapies/ procedures for treating AD and conditions other than AD, for the safety analysis set.

- Summary of prior non-drug therapies/procedures related to AD by SOC and PT.
- Summary of prior non-drug therapies by SOC and PT for treating conditions other than AD.

- Summary of concomitant non-drug therapies by SOC and PT for treating conditions other than AD.

A listing will be provided for non-drug therapies and procedures. The listing will include reported term, dictionary terms, Indication, start date, study day onset (defined similarly as for medications in above section), end date and end study day (defined similarly as for medications in above section).

6.6 Participant Disposition

Summaries will be provided for the following data for the full study sample (i.e., all screened participants who signed informed consent):

- The number and percentage of participants screened, and who failed screening, along with the reasons for screen failure. (This will be reported only in the overall group.)
- The number and percentage of participants included in the treatment group as well as in each study analysis set.
- The number and percentage of participants who completed the 4 week dosing period, discontinued the 4 week dosing period with the reason for discontinuation, completed the 12 week treatment period, discontinued 12 week treatment period with reason for discontinuation, completed the study, and discontinued the study with reason for discontinuation.

A summary will be provided for major protocol deviations by deviation category.

The following listings will be provided.

- The participant disposition listing comprises various details, including the date of ICF signing, ICF and protocol versions, enrolment or screen failure dates, and the completion/discontinuation date of the 4-week dosing period, date of 12-week treatment period/discontinuation, reason for discontinuation, study completion status, date of study completion, among other factors.
- A listing of screen failures with inclusion criteria not met and/or exclusion criteria met.
- Listing of protocol deviation.

6.7 Treatment Exposure and Compliance

A descriptive summary of treatment exposure will be provided on safety analysis set for the following data.

- summary of dose administered (in mg) by visit
- summary for dose-weight proportion with the categories; [redacted].
- The number (%) of participants who receive treatment by treatment duration (≥ 15 days and ≥ 29 days)
- Number and percentage the participants with infusion frequency (1, 2 and 3 infusions).
- Summary on overall duration of the treatment.

Overall duration of the treatment will be provided irrespective of intermittent dose interruptions. The duration of treatment exposure in the study is calculated in days as:

[redacted]

Categorical summary of visit wise treatment compliance showing the number (n) and percentage of participants falling within the following ranges: <80%, 80%-<100%,100%-120%, >120% will be presented for the treatment group. The compliance with protocol-defined investigational product will be calculated as follows: Treatment Compliance= ((Actual total dose administered) / (total planned dose)) x 100%.

A listing of treatment exposure will be provided on safety analysis set, which includes start and date/time of infusion, infusion administered arm, dose, infusion rate, dose interruption, and details of dose interruption.

6.8 Analysis of Efficacy Variables

All the efficacy evaluations will be performed on modified full analysis set unless otherwise specified.

6.8.1 Analysis of Secondary Efficacy Variable

A descriptive summary (n, mean, median, standard deviation, minimum, maximum, Q1, Q3, standard error) will be provided for percentage change from baseline in EASI score at Week 12.

A mixed model repeated measure (MMRM) analysis will be performed for percentage change from baseline in EASI over time up to Week 12 by considering visit as a fixed effect, along with baseline EASI score as a covariate; unstructured covariance matrix will be used for the model errors (Alternative covariance matrices such as Compound symmetry will be used if the unstructured covariance matrix fails to converge) and Kenward-Roger (KR) approximation is used to estimate denominator degrees of freedom.

MMRM will compare the effect of IMG-007 at each post baseline visit versus the baseline based on difference relative to zero. Least square means and their corresponding 95% confidence intervals will be provided along with the p-value at nominal two-sided 5% significance level.

Based on the estimand framework introduced in ICH E9 (R1), additional details relating to the definition of the estimand is proposed.

Handling of intercurrent events of treatment discontinuation and rescue medication:

- [redacted]
- [redacted]

Handling of missing data

No missing data will be imputed for the main efficacy analysis.

Sensitivity analyses

The following two sensitivity analyses will be performed:

[redacted]

Line graphs will be generated to illustrate the change from baseline and percentage change from baseline (up to week 12) in the total EASI scores.

Note: Refer the Appendix 12.7 for the details on the management of intercurrent events and details on primary and sensitivity analysis illustrated with some examples.

6.8.2 Analysis of Key Exploratory Efficacy Variables

6.8.2.1 Continuous efficacy endpoints

All continuous exploratory efficacy endpoints will be analyzed using the same approach as that used for the main analysis of percentage change from baseline in EASI at Week 12.

For the timepoints beyond Week 12, separate MMRM models will be developed to include all the post-baseline visits until Week 24/EOS. However, the estimates and p-values will be reported only for the timepoints beyond Week 12 from these models. The results of earlier timepoints will be reported from the models up to Week 12.

Sensitivity analyses

[redacted]

Line graphs will be plotted to illustrate the change from baseline and percentage change from baseline (up to week 24) in the total EASI scores. Similar line graphs will be presented for SCORAD and O-SCORAD. The X-axis will represent visit, while the Y-axis will denote the change from baseline or percentage change from baseline.

6.8.2.2 Responder type (binary) efficacy endpoints

The responder type (binary) endpoints will be reported using frequency and percentage along with the 95% Clopper-Pearson exact confidence interval for the proportion. A nominal two-sided 5% significance level will be used.

Based on the estimand framework introduced in ICH E9 (R1), additional details relating to the definition of the estimand is proposed.

Handling of intercurrent events (for responder type binary endpoints) of treatment discontinuation and rescue medication:

- [redacted]
- [redacted]

Handling of missing data

After the handling of intercurrent events explained above, missing data will be managed in two steps as given below.

1) Non-responder imputation will be performed for all scheduled visits following participant discontinuation from the study with the reason ‘lack of efficacy’.
2) LOCF approach will be applied for all missing visits, except for missing data that arises following study discontinuation with reason 'lack of efficacy'.

Sensitivity analyses

No prespecified sensitivity analyses will be performed. Post-hoc sensitivity analysis will be considered as appropriate later.

Bar plots will be included to depict responder-type of endpoints of EASI and IGA. The X-axis will feature visits, and the Y-axis will represent the proportion of participants, expressed as a percentage.

6.8.3 Analysis of Other Exploratory Efficacy Variables

All the continuous exploratory variables will be analyzed using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

All the binary exploratory variables will be summarized with frequency and percentages.

No missing data imputations and sensitivity analysis are applicable for other exploratory endpoints.

6.9 Analysis of Safety Data

The summary of safety will be performed based on safety analysis set.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, physical examination, vital signs, and 12-lead ECG.

6.9.1 Analysis of Adverse Events

Incidence tables for both non-TEAEs and TEAEs will be presented. The table will include the number (n) and percentage (%) of participants who are experiencing an adverse event, along with the corresponding number of episodes of AEs. Participants with multiple adverse events in a particular category will be counted only once in that category. Participants with multiple severities/grading will be counted only once under maximum severity/grading.

The number and proportion of participants reporting non-TEAEs/TEAEs will be summarized, sorted by decreasing frequency of SOC and PT, and in case of further ties, then alphabetically.

Listings will be provided by SOC and PT, for non-TEAEs, TEAEs and TESAEs, TEAEs of infusion related reactions, and TEAEs leading to study treatment discontinuation.

The following summaries will be provided for the adverse events.

- Overall summary of AEs: The overall summary of AEs will be provided with number and proportions of participants with any:
    - non-TEAE
    - TEAE
    - Related TEAE
    - SAE
    - TEAE by CTCAE grades
    - TEAE that are infusion related reaction
    - TEAE leading to 4-week dosing period discontinuation
    - TEAE leading to 12-week dosing period discontinuation
    - TEAE leading to study discontinuation
    - TEAE with outcome of death
- Summary of non-TEAEs by SOC and PT
- Summary of TEAEs by SOC and PT
- Summary of TEAE occurred during treatment period by SOC and PT
- Summary of TEAEs occurring for at least 2 participants by PT
- Summary of Serious TEAEs by SOC and PT
- Summary of TEAEs by PT and worst CTCAE grade
- Summary of TEAEs with CTCAE grade 3 or higher by PT
- Summary of treatment related TEAEs by SOC and PT

6.9.2 Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results. Summaries of laboratory variables will include:

- Descriptive statistics of continuous laboratory result and change from baseline by visit
- Number (n) and percentage (%) of participants for categorial lab data (urinalysis)
- The number (n) and percentage (%) of participants with abnormal lab value during study using a shift table
- Number (n) and percentage (%) of participants with CTCAE grade for key hematology parameters (white blood cell [WBC], neutrophils, lymphocytes, platelet, and hemoglobin)
- Number (n) and percentage (%) of participants with CTCAE grade for key serum chemistry parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum creatinine, and bilirubin)
  Note: When participants have multiple CTCAE grades within the same parameters, the worst CTCAE grade will be considered. Refer Appendix 12.8 for more details on CTCAE grading.

Listing of all laboratory parameters original results, standard results, normal range, abnormal flag and CTCAE grade (wherever applicable) by participant and visit will be provided. Additionally, listings will be provided for pregnancy test, tuberculosis test, and virology test.

A line graph illustrating absolute values for key parameters will be presented by visit.

6.9.3 Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variables and change from baseline by visits/timepoints
- Notable findings in vital signs will be summarized by visit/timepoint, which are defined as,
    - Temperature: >39.0 degrees
    - An increase in Pulse Rate from baseline by ≥25% for on-treatment values >100 beats/min
    - A decrease in Pulse Rate from baseline by ≥25% for on-treatment values <50 beats/min.
    - Systolic BP≥ 140 mmHg and increase by 20 mm Hg.
    - Diastolic BP≥ 90 mmHg and increase by 10 mm Hg.
    - Systolic BP≤ 80 mmHg and decrease by 20 mm Hg.
    - Diastolic BP≤ 50 mmHg and decrease by 10 mm Hg.

A listing of vital signs data will be provided for each participant by visit.

6.9.4 Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters by visit will include:

- Descriptive statistics of actual and change from baseline.
- ECG status (i.e., normal, abnormal) summarized by a shift table
- Notable findings in ECG, which are defined as:
    - a new onset in the QT interval >500 ms
    - a new onset in the QTcF interval >500 ms
    - an increase from baseline in QTcF >60 ms
    - an increase in heart rate from baseline by ≥25% for on-treatment values >100 bpm
    - a decrease in heart rate from baseline by ≥25% for on-treatment values <50 bpm
    - an increase in PR interval from baseline by ≥25% for on-treatment values >200 ms
    - an increase in the QRS interval from baseline by ≥10% for on-treatment values >110 ms, any time on treatment.

A listing will be provided for each participant by visit.

6.9.5 Physical Examination

Results from physical examinations will be listed by participant at each visit.

6.10 Analysis of Pharmacokinetic Data

A descriptive summary of serum concentration data will be presented. Serum concentration will be listed for each participant by visit.

Following figures will be provided for the serum concentration data,

- Mean (±SD) serum concentration vs time profile: Linear scale
- Mean (±SD) serum concentration vs time profile: Semi-log scale
- Individual serum concentrations vs time profile: Linear scale

- Individual serum concentrations vs time profile: Semi-log scale

6.11 Analysis of Pharmacodynamic Data

Pharmacodynamic data (including data from biopsies) will be made available during the time of clinical database lock. Descriptive statistics of the following variables will be presented.

- Listing of TARC concentration by visit
- Summary of TARC concentration change from baseline over time
- Listing of RO by visit
- Summary of RO change from baseline over time
- Listing of OX40+/CD4+ percentage by visit
- Summary of OX40+/CD4+ percentage change from baseline over time
- Listing of Percentage of K16-positive cells in the epidermis by visit
- Summary of Percentage of K16-positive cells in the epidermis change from baseline over time
- Listing of the number of OX40 positive cells by visit
- Summary of the number of OX40 positive cells change from baseline over time
- Listing of the number of OX40L positive cells by visit
- Summary of the number of OX40L positive cells change from baseline over time
- Listing of skin thickness by visit
- Summary of skin thickness change from baseline over time
- Summary of eosinophil change from baseline over time

[redacted]

6.12 Analysis of Immunogenicity Data

The ADA variables will be summarized using descriptive statistics in the immunogenicity analysis set. Frequency tables of the proportion of participants developing ADA positivity in the ADA assay, pre-existing ADA, treatment-emergent, treatment-boosted, persistent, indeterminate and transient ADA responses will be presented as absolute occurrence (n) and percent of participants (%).

Listing of ADA data will be provided.

The following summaries will be performed on the immunogenicity analysis set:

- Number (%) of patients negative ADA at all the time points analyzed
- Number (%) of patients ADA positive at time points analyzed
- Number (%) of patients with pre-existing ADA, treatment-emergent ADA, and treatment boosted ADA response
- Number (%) of patients with persistent, transient and indeterminate treatment-emergent ADA response
- Descriptive statistics of PK concentration in ADA positive and ADA negative participants.

7. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

7.1 Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of study drug (Week 0 (Day 1)). When it is not possible to determine the time of assessment, baseline value would be determined based on the measurement recorded on the day administration of the first dose of IMP.

7.2 Data Handling Convention Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as "severe" in the frequency tables by intensity of TEAE. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as "related" in the frequency tables by relation to the investigational product.

The partial date values will be imputed as specified in the Appendix 12.2. Imputed dates will not be presented in the listings.

7.3 Analysis Visit Window

For summaries that include data collected over multiple visits, where appropriate, the data will be summarized by analysis visit window. If there are multiple measurements within a scheduled visit window (refer Appendix 12.6), the closest measurement to the scheduled timepoint of the visit will be used in the analysis. If there are two observations which have the same difference in days to the planned day, but which are not measured on the same day, the later value will be selected. If there is more than one observation on the same day then;

- Latest value will be considered in all cases except for vital signs, ECG.
- Average value will be considered in cases of continuous vital signs and ECG parameters.
- The worst value will be considered for ECG interpretation.

All measurements will be presented in the listing.

8. INTERIM ANALYSIS

[redacted]

[redacted]

All analysis in which inferential statistics will be generated will be interpreted using the two-sided nominal alpha of 0.05.

8.1 Interim Efficacy Analyses

[redacted]

8.2 Interim Safety Analyses

[redacted]

[redacted]

9. SAFETY REVIEW COMMITTEE

A safety review committee (SRC) consisting of three independent physicians will be convened to review safety data, dose escalation criteria, and the study stopping criteria. A SRC will be convened to review safety data and the study stopping criteria.

9.1 SRC Efficacy Analyses

Efficacy data to be presented in the SRCs will include the following:

- Mean and mean % change from baseline in EASI by visit

9.2 SRC Safety Analyses

Safety data to be presented in the SRCs will include the following:

TEAE

- Overall summary of TEAE
- Summary of TEAEs by SOC and PT
- Summary of Serious TEAEs by SOC and PT
- Summary of TEAEs with CTCAE grade 3 or higher by PT
- Summary of treatment related TEAEs by SOC and PT

Lab values

- Number (n) and percentage (%) of participants with CTCAE grade for key hematology parameters (WBC, neutrophils, lymphocytes, eosinophils, platelet, and hemoglobin)
- Number (n) and percentage (%) of participants with CTCAE grade for key serum chemistry parameters (ALT, AST, serum creatinine, and bilirubin)

Vital signs

- Notable findings in vital signs

ECG

- Notable findings in ECG

10. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

11. REFERENCES

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12. APPENDIX

12.1 Schedule of Assessments

Procedures	**Screening**	**Treatment Period**							**Follow-up Period**		
		Baseline						**EOT**[13]			**EOS**[13]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
		Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24
	Day -35 to -1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169
Time window			± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d
Informed consent[1]	X										
Demographics and medical history[2]	X										
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X						X			X
Inclusion/exclusion criteria	X	X									
Prior and concomitant therapies	X	X	X	X	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X	X	X	X	X
Hematology and blood chemistry[5]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X		X	X			X			X
TB testing and TB risk follow up[6]	X							X			X
Viral disease screening[7]	X										
Pregnancy tests (WCBP only)[8]	X^{S}	X^{S+U}	X^{S}	X^{S+U}	X^{S+U}		X^{S}	X^{S}	X^{S}	X^{S}	X^{S}
Administration of study treatment[9]		X		X	X						
EASI, IGA, SCORAD[10]	X	X	X	X	X	X	X	X	X	X	X
Itch and sleep quality NRS, PGIS[11]	X	X	X	X	X	X	X	X	X	X	X
PGIC[11]			X	X	X	X	X	X	X	X	X

Procedures	**Screening**	**Treatment Period**							**Follow-up Period**		
		Baseline						**EOT**[13]			**EOS**[13]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
		Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24
	Day -35 to -1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169
Time window			± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d
DLQI[12]		X			X		X	X	X	X	X
AD lesion photograph (optional)		X						X			X
PK sampling		X	X	X	X	X	X	X	X	X	X
ADA sampling		X		X	X	X	X	X	X	X	X
Receptor occupancy and TARC		X	X	X	X	X	X	X	X	X	X
Skin biopsy (optional)		X						X			X

1. Study-specific procedures will be performed after receipt of signed informed consent.
2. Medical history includes prior/concurrent relevant conditions and medications, prior/current AD treatment, and surgical history. At the Baseline visit, medical history is updated prior to administration of study treatment.

   Demographics include date of birth, gender, race and ethnicity, height, and body weight. BMI will be calculated as weight (kg) / [height (m) x height (m)].
3. Vital signs include respiratory rate, blood pressure, pulse, and body temperature. On study treatment dosing days, i.e., Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29), vital signs should be assessed 15 (± 5) minutes before initiation of infusion; 15 (± 5) minutes after the initiation of the infusion; 15 (± 5) minutes after EOI, and 1 hour (± 15 minutes) post EOI. Participants need to rest for 5 minutes before having their vital signs measured.
4. Physical examination: A full physical examination will be performed at Screening. A brief physical examination will be completed at the Baseline visit, and symptom-directed physical examinations will be completed at each follow-up visit at the discretion of the investigator.
5. Laboratory assessments will be analyzed at a central laboratory. If lab test results do not meet the inclusion/exclusion criteria at Screening, a repeat test may be performed.
6. All participants will undergo TB test (QuantiFERON-TB Gold [QFT-G] test or an equivalent test) at a central or local laboratory at Screening. Participants who receive study treatment will be followed up by a TB risk assessment questionnaire (see Appendix 1) at Week 12 and Week 24/EOS. If the participants have a negative TB test at the initial screening evaluation, the TB test could be waived at the rescreening if no changes in the participant's medical history that warrant retesting, and no more than 90 days have passed.
7. Viral disease screening includes HBsAg, HBsAb, HBcAb, HCV antibody and HIV antibody. Participants who do not complete the viral disease screening test before the execution of V3.0 protocol should request testing at one of the subsequent visits through a central or local laboratory as feasible.
8. Pregnancy tests are only for women who are of childbearing potential. Serum hCG will be performed at the Screening, Baseline (Day 1), Week 1 (Day 8), Week 2 (Day 15), Week 4 (Day 29), and at the selected follow-up visits. In addition, a urine pregnancy test must be performed prior to dosing on Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29), which will be conducted at the study site.
9. On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes with a slower rate during the first 15 minutes. Participants will be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AEs observed have resolved or stabilized, whichever is longer. For diagnostic purposes, any participant who experiences any systemic infusion-related event should have a blood sample taken ideally 30–60 minutes after the onset for tryptase testing and samples may be analyzed

by a central or local laboratory. Study sites should have access to equipment or facilities for the management of potential hypersensitivity reactions. On dosing days, study treatment infusion should be performed after other study assessments have been performed. The study site will contact participants by telephone approximately 24 hours after the infusion for general AE query.

10. EASI, IGA, and SCORAD (extent of disease and disease severity) should be performed by the investigator. Efforts should be made that the same assessor performs the assessments of a particular participant throughout the study.
11. Participants will complete a worst itch and sleep quality NRS questionnaire with a 7-day period recall immediately prior to the visit day, and questionnaires for PGIS of AD and PGIC of AD. Participants should be reminded to answer all the questions.
12. Participants will complete the DLQI questionnaire to measure how much his/her skin problem has affected his/her life over the last week. Participants should be reminded to answer all the questions.
13. Participants who discontinue study treatment early (before completing the 4-week dosing period) should continue with all the remaining study visits. Participants who withdraw from the study any time before the Week 12 visit should complete the Week 12 (Day 85)/EOT visit at withdrawal. Participants who withdraw from study early after Week 12 should complete the Week 24 (Day 169)/EOS visit at withdrawal.

Abbreviations: AD = atopic dermatitis; ADA = anti-drug antibody; AE = adverse event; BMI = body mass index; CRP = C-reactive protein; DLQI = dermatology life quality index; EASI = eczema area and severity index; ECG = electrocardiogram; EOI = end of infusion; EOS = end of study; EOT = end of treatment; HBcAb = antibody to hepatitis B core antibody; HBsAb= hepatitis B surface antibody; HBsAg= hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = investigator's global assessment; IV = intravenous; NRS = numerical rating scale; PGIC = patient global impression of change in AD; PGIS = patient global impression of severity of AD; PK = pharmacokinetic; S = serum; SCORAD = scoring atopic dermatitis; TARC = thymus- and activation-regulated chemokine; TB = tuberculosis; U = urine; V = visit; WCBP = women of childbearing potential

12.2 Partial Date Conventions

Algorithms for Adverse Events, Medical History, and Prior and Concomitant Medications

Partial date to be imputed as:

Start Date	**Stop Date**	**Action**
Complete	Complete	No action
Partial, but known components shows it can't be on or after study medication start	Complete	Impute the start date as "01", if only the day is missing. Impute the start date as "01 January", if month and day are missing.
	Date and/or month missing	Impute the stop date as the latest possible date (i.e., last day of the month, if only the day is missing or "31 December" if month and day are missing).
Partial, could be on or after the study medication start Or missing	Complete	1) If stop date < study medication start then, Impute the start date as earliest possible date (i.e., "01", if only the day is missing or "01 January", if month and day are missing). 2) If stop date >= study medication start then, impute the start date equal to the study medication start date.
	Partial	Impute the stop date as the latest possible date (i.e., last day of the month, if only the day is missing or "31 December" if month and day are missing). then, 1) If stop date < study medication start then, impute earliest possible date. 2) If stop date >= study medication start, then impute the start date equal to the study medication start date.
	Missing	Missing date will not be imputed.

12.3 Eczema Area and Severity Index (EASI)

The EASI scoring system uses a defined process to grade the severity of the signs of eczema and the extent affected:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a **score between 0 and 6** based on the percentage involvement. Precise measurements are not required.

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Grade the severity of each sign on a scale of 0 to 3:

- ☐ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present, it should be at least mild (1)
- ☐ Palpation may be useful in assessing edema/papulation as

How to record your scores

The assessed parameters are inserted into a table (example shown below for age≥8 years).
The final EASI score ranges from 0-72.

Body region	**Erythema**	**Edema/ papulation**	**Excoriation**	**Lichenification**	**Area score**	**Multiplier**	**Score**
Head/neck	**(** +	+	+	**)**	**X**	**X 0.1**	
Trunk	**(** +	+	+	**)**	**X**	**X 0.3**	
Upper extremities	**(** +	+	+	**)**	**X**	**X 0.2**	
Lower extremities	**(** +	+	+	**)**	**X**	**X 0.4**	
The final EASI score is the sum of the 4 region scores							**_____ (0-72)**

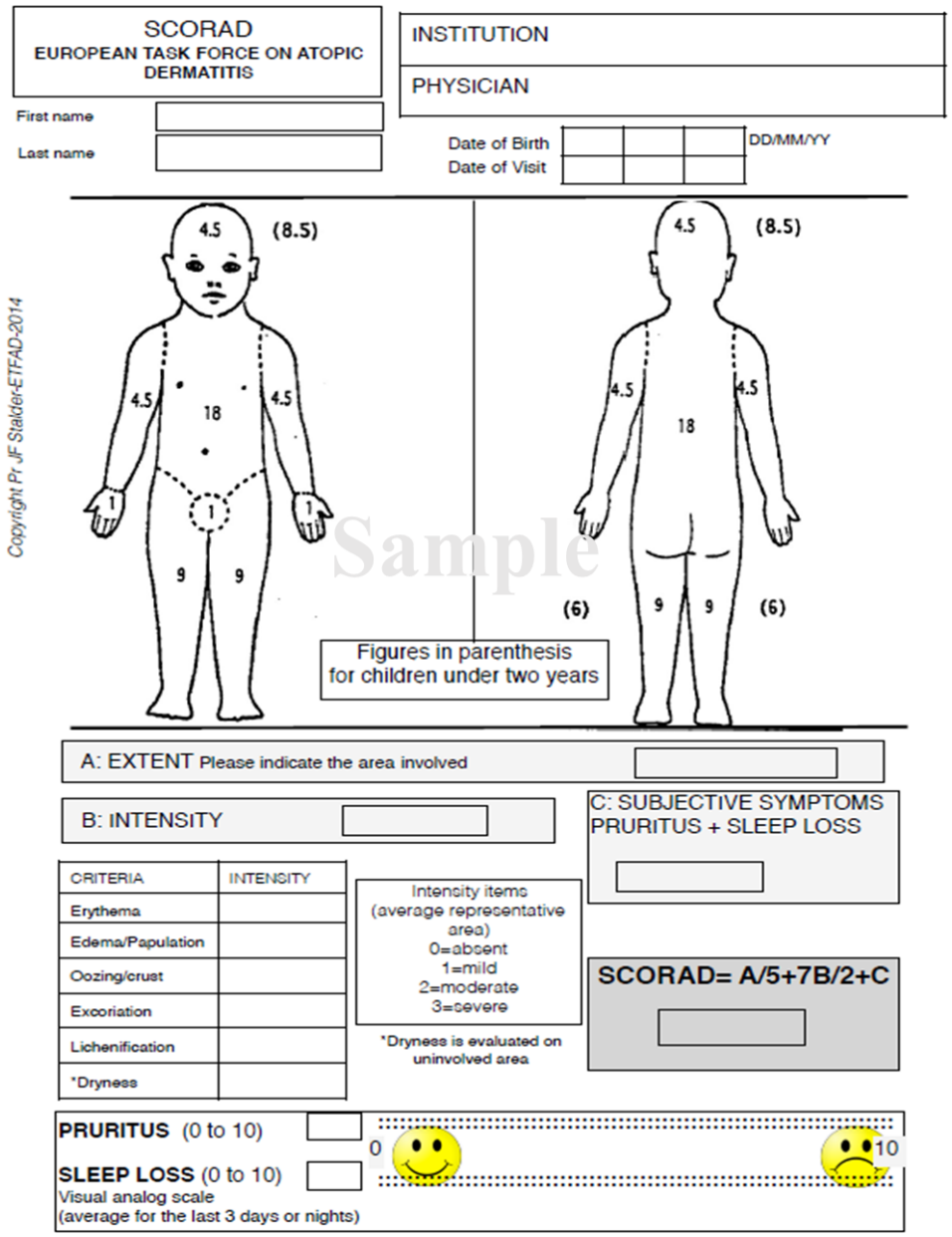
12.4 SCORing Atopic Dermatitis (SCORAD) Index

Please refer to Dermatology 1993:186:23-31. doi: 10.1159/000247298. for the assessment of SCORAD index.

Grading of Intensity Items (Objective Signs):
Six items have been selected: (1) erythema. (2) edema/papulation. (3) oozing/crusts. (4) excoriations, (5) lichenification. (6) dryness.
Each item should be graded 0-3 (0=absent; 1 = mild: 2= moderate: 3 = severe) according to reference photographs (sec 'Atlas', i.e. fig. 1-15 in Dermatology 1993:186:23-31. doi: 10.1159/000247298). Half-point scoring is not recommended. The area chosen for grading must be representative (average intensity) for each item in a given participant as determined by the investigator, thus excluding one 'target' area or the worst affected site. The same site may however be chosen for 2 or more items. For example, one site may serve for evaluation of both excoriations and erythema. On the other hand, dryness must be appreciated on areas not involved by acute lesions or lichenifications.

Grading Extent:
The rule of nine is detailed in the front-back drawing on the evaluation sheet with a variant (head and lower limbs) for participants under 2 years of age. Lesions taken into account must include only inflammatory lesions and not dryness. In practice it is recommended to draw directly the extent of individual lesions on the printed figure of the evaluation sheet. Note that one participant's palm represents 1% of his body surface.

Subjective Items:
These include pruritus and sleep loss. Make sure that the participant (generally over 7 years) or his/her parents is/arc capable of answering properly. Ask him/her to indicate on the 10-cm scale of the assessment form the point corresponding to the average value for the last 3 days/nights.


SCORAD
EUROPEAN TASK FORCE ON ATOPIC DERMATITIS
INSTITUTION
PHYSICIAN
First name
Last name
Date of Birth
Date of Visit
DD/MM/YY
Copyright Pr. JF Stalder-ETFAD-2014
4.5
(8.5)
18
9
(6)
Sample
Figures in parenthesis
for children under two years
A: EXTENT Please indicate the area involved
B: INTENSITY
C: SUBJECTIVE SYMPTOMS
PRURITUS + SLEEP LOSS
CRITERIA
INTENSITY
Erythema
Edema/Papulation
Oozing/crust
Excoriation
Lichenification
*Dryness
Intensity items
(average representative area)
0=absent
1=mild
2=moderate
3=severe
*Dryness is evaluated on uninvolved area
SCORAD= A/5+7B/2+C
PRURITUS (0 to 10)
SLEEP LOSS (0 to 10)
Visual analog scale
(average for the last 3 days or nights)
0
10

12.5 Handling of items from DLQI

I. If one question is left unanswered this is scored 0 and the scores are summed up and expressed as usual out of a maximum of 30.
II. If two or more questions are left unanswered the questionnaire is not scored.
III. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
IV. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1.
V. If two or more response options are ticked for one question, the response option with the highest score (i.e., worst) should be recorded.
VI. The DLQI can be analyzed by calculating the score for each of its six sub-scales. When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

12.6 Analysis Visit Window

Analysis Visit	Target Day	Group 1	Group 2	Group 3*	Group 4	Group 5	Group 6
Baseline	1	Up to day 1	-	Up to day 1	Up to day 1	Up to day 1	Up to day 1
Week 1	8	2-11	2-11	-	-	-	
Week 2	15	12-22	12-22	2-22	2-22	-	2-22
Week 4	29	23-36	23-36	23-57	23-43	2-43	23-43
Week 6	43	37-50	37-50	-	-	-	-
Week 8	57	51-64	51-64	-	44-64	44-64	44-64
Week 12	85	65-92	65-92	58-127	65-92	65-92	65-92
Week 16	113	93-120	93-120	-	93-120	93-120	93-120
Week 20	141	121-148	121-148	-	121-148	121-148	121-148
Week 24	169	149-172	149-172	128-172	149-172	149-172	149-172

Group 1: Vital signs, Physical examination, Adverse events, Prior and concomitant therapies, Hematology, blood chemistry, EASI, IGA, SCORA, Itch and sleep quality NRS, PGIS, PK sampling, Receptor occupancy and TARC.
Group 2: PGIC
Group 3: Urinalysis
Group 4: Pregnancy test
Group 5: DLQI.
Group 6: ADA sampling
*Use group 3 for ECG and TB assessment by removing week 2 and week 4 and changing the Week 12 window from ’58-127’ to “2-127”.

12.7 Statistical Consideration of Intercurrent Events

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.8 CTCAE Version 5.0 for Key Hematology and Serum Chemistry Parameters

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	