Clinical Study Protocol

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
Protocol Version:	Version 7.0
Version Release Date:	14 June 2024
Development Phase:	1b/2a
Sponsor:	Inmagene LLC
Sponsor Address:	12526 High Bluff Drive, Suite 345, San Diego CA, 92130, USA
EU CT Number:	2023-505735-13
IND Number:	159690

This study is to be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements.

SPONSOR INFORMATION PAGE

Sponsor Contact

Inmagene LLC, 12526 High Bluff Drive, Suite 345, San Diego, CA 92130, USA

In some countries, the clinical trial sponsor may be the local affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Global Medical Monitors Contact Information:

Information can be found in the site binder.

Report serious adverse events within 24 hours via email/fax provided in the site manual.

SPONSOR SIGNATORY

Protocol Version: 7.0
Protocol Date: 14 June 2024

[redacted]
Inmagene LLC

Date

COORDINATING INVESTIGATOR SIGNATORY

Protocol Version: 7.0
Protocol Date: 14 June 2024

The study will be conducted in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Institution: University Hospital Frankfurt

Location: Germany

Coordinating Investigator:

[redacted]	[redacted]
Print Name	Title
Signature	Date

INVESTIGATOR

I have read and agree to the protocol IMG-007-201 titled "A Phase 1b/2a Study to Evaluate the Safety, Pharmacokinetics and Efficacy of IMG-007 in Adult Participants with Moderate-to-Severe Atopic Dermatitis" Version 7.0, 14 June 2024. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice, Declaration of Helsinki, local regulations (as applicable) and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Institution:

Location:

Investigator:

Print Name	Title
Signature	Date

PROTOCOL AMENDMENT DETAILS

History of Amendments

[redacted]

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

Summary of changes in the current amendment:

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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LIST OF ABBREVIATIONS

Term	Definition
AD	Atopic Dermatitis
ADA	Anti-drug Antibody
ADCC	Antibody-dependent Cellular Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
$AUC_{\tau,SS}$	Area Under the Concentration-time Curve from Time 0 to τ (the Dosing Interval) at Steady State
BSA	Body Surface Area
CL	Central Compartment Clearance
C_{max}	Peak Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Event
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
EC_{90}	90% Maximal Effective Concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOI	End of Infusion
EOS	End of Study
EOT	End of Treatment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
IA	Interim Analysis
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee

Term	Definition
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IL	Interleukin
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JAK	Janus Kinase
mAb	Monoclonal Antibody
MMRM	Mixed Models for Repeated Measures
NCI	National Cancer Institute
NOAEL	No-Observed-Adverse-Effect Level
NRS	Numerical Rating Scale
OX40L	OX40 Ligand
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetics
QoL	Quality of Life
RO	Receptor Occupancy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SoA	Schedule of Assessments
SQ-NRS	Sleep Quality Numerical Rating Scale
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus- and Activation-regulated Chemokine
TB	Tuberculosis
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroid
TEAE	Treatment-emergent Adverse Event
ThX	T Helper X
TNFR	Tumor Necrosis Factor Receptor
ULN	Upper Limit of Normal
UV	Ultraviolet
Vc	Central Compartment Volume
WHODrug	World Health Organization Drug Dictionary
WI-NRS	Worst Itch Numerical Rating Scale

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: Inmagene LLC	**Protocol Number:** IMG-007-201
Investigational Product: IMG-007, a humanized anti-OX40 immunoglobulin G1 monoclonal antibody (mAb)	**Phase of Development:** 1b/2a
Route of Administration: Intravenous (IV) infusion	**Date of Protocol:** 14 June 2024
Protocol Title: A Phase 1b/2a Study to Evaluate the Safety, Pharmacokinetics and Efficacy of IMG-007 in Adult Participants with Moderate-to-Severe Atopic Dermatitis	
Number of Participants: Approximately 55 participants	
Study Centers: Multicenter	

Study Objectives:

Primary Objective

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

Secondary Objectives

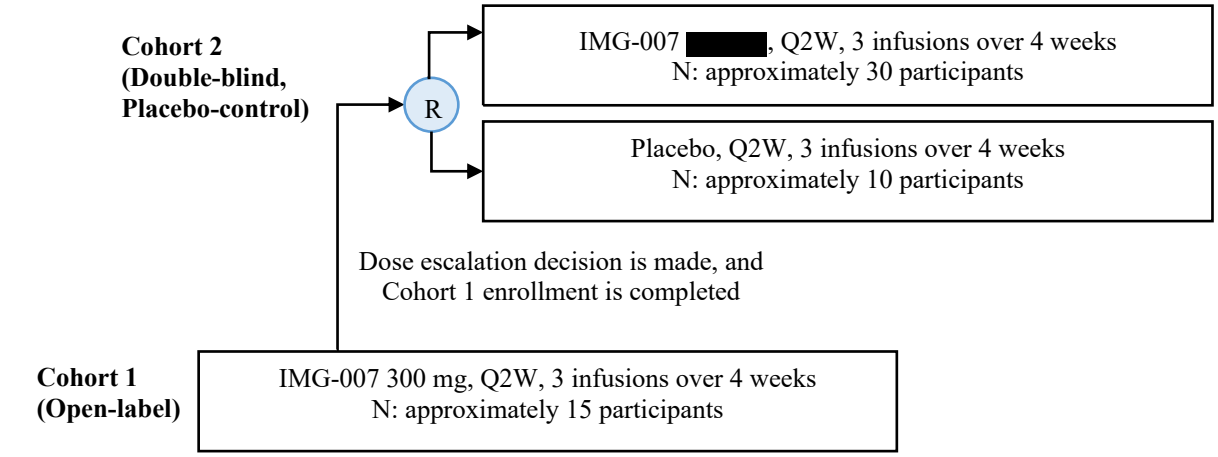
- To evaluate the efficacy of multiple doses of IMG-007 in AD participants as measured by eczema area and severity index (EASI) at Week 12

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 (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 characterize the pharmacokinetic (PK) profile 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

Study Design:

This 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 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]



R = Randomization

- **Screening Period**: Day -35 to Day -1 (up to 5 weeks): After providing informed consent, participants will be assessed for compliance with protocol requirements and study eligibility.
- **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). The study site will contact participants by telephone approximately 24 hours after each infusion for assessments of AE and/or concomitant medications.

  On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes at 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 during the observation 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.

  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: Week16 (Day 113), Week 20 (Day 141) and Week 24 (Day 169)/end of study (EOS) visits.

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 the study early after Week 12 should complete the Week 24 (Day 169)/EOS visit at withdrawal.

Background Non-pharmacological Therapy

All participants will apply a non-medicated emollient (moisturizer) twice daily starting at least one week before the Baseline visit and throughout the study.

Concomitant Medications

Oral antihistamines are allowed. Topical and systemic medications for the treatment of AD are prohibited during the study. If medically necessary (i.e., to control intolerable AD symptoms), rescue treatment may be prescribed to study participants at the discretion of the investigator. [redacted]

[redacted] Rescue medications will not be provided by the Sponsor.

The study enrolled a total of 13 participants into Cohort 1 between July 18, 2023, and January 31, 2024. On March 18, 2024, the sponsor decided to terminate further screening and enrollment of patients into the study. The decision was made because of slower than expected enrollment and the expectation that data from Cohort 1, despite being a small open-label cohort, will provide valuable information to inform the design of a more robust Phase 2b study. . No safety concerns were noted. Therefore, the design and description related to Cohort 2 in this protocol is no longer applicable.

Safety Monitoring and Dose Escalation:

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

AE severity will be evaluated according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

The medical monitors from the contract research organization (CRO) and the Sponsor will confirm and document in the study file the dose escalation decision before the dosing in the subsequent cohort can proceed.

Study Treatment Discontinuation Criteria

[redacted]

Dose Escalation Criteria

[redacted]

Study Stopping Criteria

[redacted]

[redacted]

Study Population:

The study population includes adults with moderate-to-severe AD. Eligibility criteria include the following:

Inclusion Criteria

1) Male or female aged ≥ 18 and < 75 years.
2) Able to participate and comply with all study procedures and restrictions, and willing to provide written informed consent to participate in the study.
3) Diagnosed with AD for [redacted] according to the American Academy of Dermatology Consensus diagnostic criteria (Eichenfield et al. 2014) at the Screening visit.
4) Moderate-to-severe AD, defined as:
   a) EASI score ≥ 12 at the Screening visit and ≥ 16 at the Baseline visit
   b) IGA ≥ 3 at the Screening visit and the Baseline visit
   c) Body surface area (BSA) ≥ 10% at the Screening and the Baseline visits
5) Documented history of inadequate response or lack of tolerability, as assessed by the investigator, to a stable regimen (≥ 4 weeks) of one or more topical treatment, e.g., topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs) before the Screening visit, or for whom topical treatments are otherwise inadvisable.
6) Agree to apply a stable dose of a non-medicated emollient (moisturizer) twice daily at least one week before the Baseline visit and throughout the study.
7) Female participants who are not pregnant or breastfeeding and meet at least one of the following conditions:
   a) Not of childbearing potential as described in Section 5.3.
   b) Of childbearing potential and agrees to use a highly effective method of contraception as described in Section 5.3 consistently from signing of informed consent until 6 months after the last dose of study treatment. Contraception requirements do not apply to participants in an exclusively same-sex relationship. Female participants should not donate eggs until 6 months after the last dose of study treatment.
8) Male participants must be surgically sterilized (performed at least 6 months prior to the Baseline (Day 1) visit and documented to no longer produce sperm); or from signing of informed consent until at least 6 months after the last dose of study treatment, agree to use highly effective methods of contraception as described in Section 5.3 with female partners of childbearing potential during the study and must also agree not to donate sperm during this period.

Exclusion Criteria

1) Severe cardiovascular, pulmonary, renal, autoimmune and metabolic illness(es), or any other acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into the study.
2) History of clinically significant abnormal laboratory values, as determined by the principal investigator, including but not limited to the following:
   a) ALT or AST ≥ 2.5 × ULN at the Screening visit.
   b) Total bilirubin above 1.5 × ULN (unless the elevated bilirubin is related to confirmed Gilbert's Syndrome) at the Screening visit.
   c) White blood cell count < 3,000/mm^3 (< 3.0 × 10^9/L) at the Screening visit.

   Note: If the test results meet the above criteria, a repeat test may be performed to determine eligibility.
3) Positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) serology results at the Screening visit as defined below:
   a) HBV: Positive test for hepatitis B surface antigen (HBsAg), OR positive test for hepatitis B core antibody (HBcAb) with negative test for hepatitis B surface antibody (HBsAb)
   b) HCV: Positive test for hepatitis C antibody
   c) HIV: Positive test for HIV antibody
4) Evidence of active or latent tuberculosis (TB) as confirmed by the screening TB test.

5) History of untreated or inadequately treated TB infection.
6) Active infection requiring treatment with systemic antibiotics, antivirals, antifungals, antiparasitics or antiprotozoals at the Screening and the Baseline (Day 1) visit.
7) Active unstable (e.g., in an acute flare) skin conditions in addition to AD that would interfere with the assessment of AD based on the investigator's clinical judgement.
8) Use of topical treatments such as TCSs, TCIs, topical phosphodiesterase-4 inhibitors and topical janus kinase (JAK) inhibitors for AD within 2 weeks before the Baseline (Day 1) visit.
9) Use of phototherapy for AD with ultraviolet (UV) A or UVB or regular use of a tanning booth within 4 weeks before the Baseline (Day 1) visit.
10) Use of 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.
11) Use of biologic therapy including approved and investigational agents (e.g., mAbs against interleukin [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.
12) Receipt of a live (including live attenuated) vaccine within 2 months prior to the Baseline (Day 1) visit (participants must agree to avoid live [including live attenuated] vaccination during study treatment and within 3 months thereafter).
13) Any known hypersensitivity to any component of study treatment or other biologics (e.g., mAbs, fusion proteins)
14) Malignancy or a history of malignancy (exception: fully-treated skin basal cell or non-metastatic squamous cell carcinomas; or cervical carcinoma in situ with no evidence of recurrence within 5 years) prior to the Screening visit.
15) Planned major surgical procedure during the study.
16) Participation in another research study involving an investigational product within 3 months prior to the Baseline (Day 1) visit.
17) Women who are pregnant or nursing. All female participants with reproductive potential must have a negative pregnancy test prior to starting study treatment.

Study Treatment Administration:

Name of Investigational Product: IMG-007

Dosage Form: Concentrate for solution for infusion

Route of Administration: IV infusion

Doses:

- Cohort 1: three infusions of IMG-007 300 mg Q2W within 4 weeks.
- Cohort 2: three infusions of IMG-007 [redacted] or matching placebo Q2W within 4 weeks.

IMG-007 or placebo will be prepared for the desired dose and diluted with isotonic saline solution (0.9% sodium chloride marketed product) and to be administered via IV infusion.

Study Assessments:

Safety Assessments: The following safety assessments will be performed as described in the Schedule of Assessment (SoA):

- Treatment-emergent adverse events (TEAEs), treatment-emergent SAEs, TEAEs leading to treatment discontinuation.
- Vital signs, physical examination, 12-lead electrocardiogram (ECG)
- Clinical laboratory tests: hematology, serum chemistry, and urinalysis
- Pregnancy testing, if applicable
- Concomitant medications and procedures

Efficacy Assessments: The following efficacy assessments will be performed as described in the SoA:

- In-clinic assessments by the investigators including EASI, IGA, SCORAD index, and BSA

- In-clinic assessments by the patient including worst intensity itch and sleep quality due to AD over each 7-day period immediately prior to the scheduled visits, PGIS, PGIC, and DLQI
- AD lesion photography (optional, but is encouraged)

PK Assessments: Serum concentration of IMG-007 over time and by dose received will be measured using a validated method.

Immunogenicity Assessment: Anti-drug antibody (ADA) to IMG-007 will be measured using a validated method.

PD Assessments: Levels of inflammatory markers including thymus- and activation-regulated chemokine (TARC) and OX40 receptor occupancy in the blood samples and tissue biomarkers (biopsy of skin lesions is optional but is encouraged) related to OX40-OX40 ligand signaling and AD pathophysiology will be measured.

Study Endpoints:

Primary Endpoint: Incidence of TEAEs

Secondary Endpoints:

- Percentage change in EASI from Baseline to Week 12

Statistical Plan:

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]

Analysis Sets

- Safety analysis set will be used for safety analyses, which will include 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 also be used for demographic and baseline characteristics.
- Modified full analysis set will be used for efficacy analyses, which will include all participants from Cohorts 1 and 2 who received at least one dose of study treatment. Data will be analyzed by the treatment group based on the treatment assigned or randomized.
- PK analysis set will include 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 the treatment group based on the actual treatment received.
- Immunogenicity analysis set will include 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.
- PD analysis set will be used for PD analyses, which will include 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.

Statistical Methods

Unless otherwise stated, all data will be reported under the respective treatment groups (placebo, IMG-007 300 mg, and IMG-007 [redacted]). In addition, as a sensitivity analysis, data for the combined active groups of IMG-007 300 mg and [redacted] will also be reported in the tables/figures.

Safety Analyses

Safety variables including incidence and severity, and duration of TEAEs and changes from baseline of relevant parameters (e.g., vital signs, ECGs, and clinical laboratory values) will be summarized.

- AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version currently in use by the Sponsor at the time of database lock). TEAEs are defined as events started after the initiation of first dose of

study treatment or events present that worsen after the start of dosing. The number and proportion of participants experiencing one or more TEAEs will be summarized by severity, and relationship to study treatment.

- Prior and concomitant medications (including rescue medications) will be coded using the World Health Organization Drug Dictionary. The number and proportion of participants taking prior and/or concomitant medications will be summarized.
- Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) and ECG parameters will be summarized by visit descriptively. Changes from baseline, number, and proportion of participants with clinically important values will be presented descriptively.
- Clinical laboratory parameters will be summarized using descriptive statistics, by changes from baseline, post-dosing shift from Baseline (Day 1) in the normal or abnormal category of laboratory values by visit, and number and proportion of participants with a treatment-emergent clinically significant abnormal value based on predefined criteria, and data listings.

Efficacy Analyses

Continuous efficacy variables will be summarized using descriptive statistics which will include mean, median, minimum, maximum, Q1 and Q3, standard error and standard deviation. Categorical efficacy variables will be summarized by frequency and percentage for each category.

While the primary comparison of interest for efficacy endpoints will be within Cohort 2, for IMG-007 [redacted] versus placebo group, a broader comparison including 300 mg group versus placebo and the combined 300 mg and [redacted] versus placebo are also of additional, exploratory interest. For analysis within Cohort 1 (i.e., 300 mg group), efficacy comparison with baseline at each visit will be performed based on difference relative to zero. All analysis will use nominal two-sided significance level of 0.05.

For continuous efficacy endpoints, a mixed-effect model with repeated measures (MMRM) will be used. This model includes visit as a factor and respective baseline score as covariate for both Cohorts 1 & 2, and additionally treatment and treatment-by-visit interaction as factors for Cohort 2 only. Specific ways of handling data after receiving rescue medication or any other such clinical events will be performed.

For binary efficacy endpoints, if high potency corticosteroids or systemic rescue medications are used, the participant will be reported as a non-responder from the time such rescue medication is used.

Sensitivity analysis using other missing data handling approaches will also be performed. Further details including handling of specific intercurrent events and missing data imputations will be specified in the prospective statistical analysis plan (SAP).

PK Analyses

Serum concentration data will be tabulated and summarized (geometric mean, arithmetic mean, minimum, maximum, SD and % coefficient of variation) by treatment group for each visit at which samples were taken.

Immunogenicity Analyses

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of participants who develop detectable ADA. The incidence of positive ADA will be reported for evaluable participants.

PD Analyses

Biomarker data will be listed by participant and visit/timepoint. Data for skin punch biopsy will be listed and summarized by visit.

Timing of Analyses

[redacted]

1.2 Schedule of Assessments

Table 1 Schedule of Assessments

Procedures	**Screening**	**Treatment Period**							**Follow-up Period**		
		Baseline						**EOT**[17]			**EOS**[17]
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+U}	X^{S+U}		X^{S}	X^{S}	X^{S}	X^{S}	X^{S}
Randomization [9]		X									
Administration of study treatment[10]		X		X	X						
EASI, IGA, SCORAD[11]	X	X	X	X	X	X	X	X	X	X	X
Itch and sleep quality NRS, PGIS[12]	X	X	X	X	X	X	X	X	X	X	X
PGIC			X	X	X	X	X	X	X	X	X
DLQI[13]		X			X		X	X	X	X	X
AD lesion photograph (optional)		X						X			X
PK sampling [14]		X	X	X	X	X	X	X	X	X	X
ADA sampling		X		X	X	X	X	X	X	X	X
Serum biomarker sampling [15]		X	X	X	X	X	X	X	X	X	X
Whole blood sampling[16]		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 year 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 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. 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 2 (Day 15), Week 4 (Day 29), and at 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. Participants in Cohort 2 will be randomized at Baseline (Day 1) in a 3:1 ratio to receive three IV infusions of IMG-007 or matching placebo.
10. On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes at 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.
11. 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.
12. 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.
13. 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.
14. On dosing days, blood sample should be taken within 60 minutes before dosing and within 10 minutes after end of infusion.
15. Serum samples will be analyzed for peripheral inflammatory markers. On dosing days, blood sample will be taken within 60 minutes before dosing.
16. Whole blood samples will be analyzed for receptor occupancy. On dosing days, blood sample should be taken within 60 minutes before dosing and within 10 minutes after end of infusion.
17. 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; 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

2 INTRODUCTION

2.1 IMG-007

IMG-007, developed by the Sponsor, is a humanized immunoglobulin (Ig) G1 subclass monoclonal antibody (mAb) that specifically targets human OX40 with high affinity. OX40-OX40 ligand (OX40L) signaling is considered an amplifier for effector T-cell proliferation, memory T cell development and maintenance of cytokine production by T cells (Webb et al. 2016). Overactivation of this signaling is prominent in a spectrum of inflammatory and autoimmune diseases (Fu et al. 2020).

2.2 Prior Human Experience

IMG-007 has been tested in healthy participants in the clinical trial IMG-007-101. The study was a phase 1, double-blinded study to evaluate the safety, tolerability, and PK of a single ascending dose of IMG-007 in healthy participants. A total of 47 participants were randomized and included in the analysis. Of these randomized participants, 44 (93.6%) were treated with IMG-007 or placebo and all 44 treated participants completed the study. A total of 30 participants received a single dose of IMG-007, 1 to 600 mg, and 14 participants received placebo.

In total, 34 of the 44 (77.3%) participants reported at least 1 treatment-emergent adverse event (TEAE), 22 (73.3%) participants in the combined IMG-007 group and 12 (85.7%) participants in the placebo group, respectively. No death, serious adverse events (SAEs), or TEAEs leading to study discontinuation were reported. No TEAEs were judged to be drug related by the investigator. All TEAEs were of mild or moderate severity. No TEAEs were indicated as infusion site reactions or infusion associated reactions. There were no reports of pyrexia or chills. The TEAEs occurring in 2 or more participants by preferred term (PT) in the combined IMG-007 group vs. the placebo group were: dermatitis contact (20.0% vs. 21.4%), COVID-19 (16.7% vs. 0%), headache (10.0% vs. 28.6%), myalgia (6.7% vs. 7.1%), and upper respiratory tract infections (6.7% vs. 7.1%). There were no TEAEs occurring more frequently in IMG-007 than the placebo group, except for isolated COVID-19 cases with no dose-related trend. There were no treatment-related trends in the safety laboratory results, vital sign, physical examination, or ECG findings.

IMG-007 overall exhibited non-linear PK, with non-linear PK in lower doses ($<$ 30 mg) and linear PK in higher doses ($\geq$100 mg). At projected therapeutic dose levels (300-600 mg), IMG-007 demonstrated a mean terminal half-life of 31 days.

Further details can be found in the Investigator's Brochure.

2.3 Atopic Dermatitis

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 (Bieber 2021). 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) (Renert-Yuval et al. 2020).

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.

2.4 Rationale for IMG-007 in Atopic Dermatitis

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 (Fu et al. 2020). 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 (Elsner et al. 2020). 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 (Guttman-Yassky et al. 2019; Nakagawa et al. 2020; Sher 2021; Guttman-Yassky 2021). 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 (Guttman-Yassky et al. 2019).

A summary of key findings from nonclinical pharmacology and toxicology studies of IMG-007 is presented in the IB.

2.5 Study Rationale

2.5.1 Rationale for Study Design

This is a phase 1b/2a study to evaluate the safety/tolerability, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) effect of IMG-007 in the target patient population, i.e., adult participants with moderate-to-severe AD (eczema area and severity index [EASI] ≥ 16, investigator's global assessment [IGA] ≥ 3, and body surface area [BSA] ≥ 10%) who have had inadequate response to topical therapy or patients who are inappropriate for or intolerant of topical treatments. The study population represents a subset of AD patients who are candidates for systemic therapy, for which there remains a significant unmet need.

The study includes a 12-week treatment period and a 12-week follow-up period. The proposed 12-week treatment period is based on a 4-week dosing duration which is anticipated to result in a reasonable level of IMG-007 systemic exposure for an initial assessment of the efficacy and safety of IMG-007 by Week 12 (i.e., 8 weeks after the last dose of study treatment) in AD patients. Based on the observation that inhibition of OX40/OX40L for as short as 4 weeks provided clinically meaningful and durable improvements in AD for up to 18 weeks after the last dose of study treatment

(Guttman-Yassky et al. 2019; Nakagawa et al. 2020; Sher 2021; Guttman-Yassky 2021), a 12-week post-treatment follow-up period has been considered in this study to evaluate the magnitude and durability of potential clinical response. Separately, the follow-up period can also help assess the duration and reversibility of potential TEAEs, especially those with a late onset.

The efficacy measurements included in this study are typically used for assessing disease activity in adult AD participants. The primary and secondary efficacy variables include investigator-assessed EASI, IGA and scoring atopic dermatitis (SCORAD), as well as patient-reported outcomes including itch and sleep quality numerical rating scale (NRS), patient global impression of severity (PGIS) of AD, patient global impression of change (PGIC) of AD, and dermatology life quality index (DLQI). The clinical and laboratory procedures in this study are standard and generally accepted in clinical trials with a similar target population.

2.5.2 Rationale for Dose Selection

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.6 Summary of Benefits and Risks

Clinical effects of IMG-007 in patients have not been assessed. Based on clinical data from studies of other investigational products that also inhibit the OX40-OX40L signaling (Guttman-Yassky et al. 2019; Furihata et al. 2021; Guttman-Yassky et al. 2023) in AD patients, the mechanism of action and nonclinical pharmacology data of IMG-007, it is assumed that IMG-007 may exhibit potential clinical activities in AD patients.

Several investigational mAbs targeting OX40 are in clinical development. KHK4083, a fully nonfucosylated (intended for enhanced ADCC) IgG1 mAb against OX40, was evaluated in three studies in adult healthy subjects or patients with ulcerative colitis (Furihata et al. 2021) and adult AD patients (Guttman-Yassky et al. 2023) where acute injection/infusion-related reactions including chills, pyrexia, and malaise were the most reported adverse events (AEs). On the other hand, in a phase 2a study of GBR 830, a humanized mAb against OX40, in AD patients who received IV infusions of GBR 830 at 10 mg/kg or placebo on Day 1 and Day 29, the most common AEs occurring more frequently in GBR 830-treated patients versus the placebo group were postprocedural infection and myalgia (Guttman-Yassky et al. 2019).

Considering that IMG-007 is an investigational therapeutic protein, its mechanism of targeting OX40-OX40L signaling and known safety information from other investigational products with a similar mechanism of action, potential safety risks include injection/infusion site irritation, localized or systemic hypersensitivity reactions due to study treatment injection/infusion and potential immunogenicity, and infections.

IMG-007 is developed with modifications in the Fc region intended to remove glycosylation and abolish ADCC. In a single ascending dose study of IMG-007 in adult healthy participants who received a single dose of up to 600 mg, no infusion-related reactions were reported. Despite early evidence that IMG-007 may pose a relatively lower risk for infusion-related reactions, cautions will be taken by carefully escalating dose from the 300 mg to [redacted] dose level. [redacted] During this study, participants will receive IV infusions over approximately 60 minutes at a slower rate during the first 15 minutes and will be closely monitored during and after study treatment administration.

The inclusion and exclusion criteria are intended for enrollment of AD participants who are candidates for biologic therapies and for whom potential safety risks from participating in the study is considered acceptable. The overall risk to participants is minimized by excluding participants with comorbidities and/or concomitant medications that may potentially increase their risk for TEAEs during the study, such as severe infections, especially opportunistic infections. Participants will be excluded if they have any active acute or chronic infections. A tuberculosis (TB) risk assessment questionnaire (see Appendix 1) will be used for periodic screening for new or reactivated TB infection over the treatment and follow-up period. Study treatment will be discontinued in participants who develop severe infections during the study. In summary, the potential risk to participants is minimized by ensuring compliance with the inclusion/exclusion criteria and concomitant medications, timely reporting of TEAEs, and periodic monitoring of vital signs and safety laboratory values at in-clinic visits, together with a rule for discontinuation of study treatment in the event of severe/serious TEAEs. The potential risk versus benefit is supported for the study as designed.

3 STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are summarized in Table 3 .

Table 3 Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate AEs emergent from multiple doses of IMG-007 in adult participants with AD	Incidence of TEAEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of multiple doses of IMG-007 in AD participants as measured by EASI at Week 12	Percentage change in EASI from baseline to Week 12
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the efficacy of multiple doses of IMG-007 in AD participants as measured by EASI, IGA, SCORAD index, and patient-assessed itch and sleep quality NRS, PGIS of AD, PGIC of AD, and DLQI	• 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 IGA 0 or 1 (clear or almost clear) and ≥ 2-point reduction from baseline by visit • Proportion (%) of participants achieving ≥ 2-point reduction in IGA from baseline by visit • Change from baseline in percent BSA by visit • Change from baseline in SCORAD by visit • Mean and mean % change from baseline in 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 SQ-NRS 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
To further characterize safety and tolerability of multiple doses of IMG-007 in AD participants	• Incidence of TEAEs by severity and relationship to study treatment • Changes from baseline in laboratory parameters, vital signs and ECG parameters by visit • Incidence of clinically significant abnormal values in laboratory and ECG parameters by visit
To characterize the pharmacokinetic (PK) profile of multiple doses of IMG-007 in AD participants	• Mean serum concentration of IMG-007 over time
To evaluate the PD effect of IMG-007 on biomarkers in AD participants	• Changes in RO and inflammatory markers including TARC in peripheral blood over time • Changes in histopathology, transcriptomics and tissue biomarkers from baseline over time
To evaluate the immunogenicity of IMG-007 in AD participants	• Occurrence of ADA after administration of IMG-007 over time

Abbreviations: AD = atopic dermatitis; ADA= anti-drug antibody; AE = adverse event; BSA = body surface area; CL = central compartment clearance; 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; IGA = investigator’s global assessment;

NRS = numerical rating scale; PD = pharmacodynamic; PGIC = patient global impression of change; PGIS = patient global impression of severity; PK = pharmacokinetic; RO = receptor occupancy; SCORAD = scoring atopic dermatitis; SQ-NRS = sleep quality numerical rating scale; TARC = thymus- and activation-regulated chemokine; TEAE = treatment-emergent adverse event; WI-NRS = worst intensity itch numeric rating scale; Vc = central compartment volume

4 STUDY DESIGN

4.1 Overall Study Design

This 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 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]

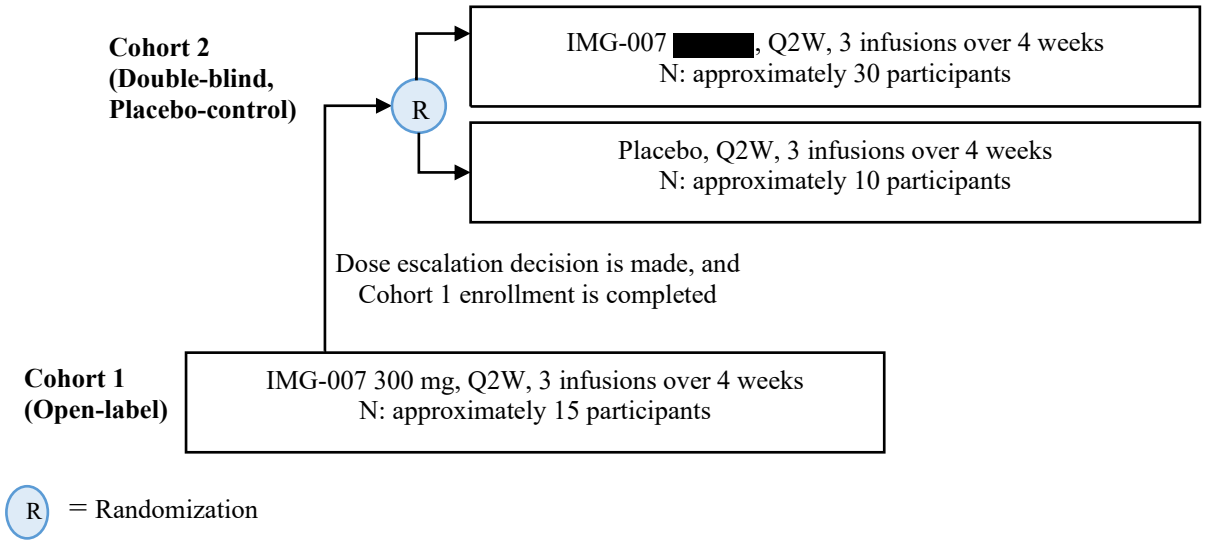


Figure 2 Study Schema

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

After providing informed consent, 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 1will 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). The study site will contact participants by telephone approximately 24 hours after each infusion for assessments of AE and/or concomitant medications.

On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes at a slower rate during the first 15 minutes. In the event of an infusion-related reaction, for the purposes of participant safety, the investigator may decide to slower the rate of infusion or suspend the dosing. Participant will be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AEs observed during the observation 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.

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 Week 24 (Day 169)/end of study (EOS) visits.

The schedule of assessments (SoA) at each visit is summarized in Table 1. Assessments of efficacy, safety and PK/PD will be conducted throughout this study. Optional skin punch biopsy samples and skin lesion photography will be collected at the Day 1 (pre-dose), Week 12 (Day 85)/EOT and Week 24 (Day 169)/EOS visits. Participation in the biopsy and photography studies is optional.

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 the study early after Week 12 should complete the Week 24 (Day 169)/EOS visit at withdrawal.

The study enrolled a total of 13 participants into Cohort 1 between July 18, 2023, and January 31, 2024. On March 18, 2024, the sponsor decided to terminate further screening and enrollment of patients into the study. The decision was made because of slower than expected enrollment and the expectation that data from Cohort 1, despite being a small open-label cohort, will provide valuable

information to inform the design of a more robust Phase 2b study. No safety concerns were noted. Therefore, the design and description related to Cohort 2 in this protocol is no longer applicable.

4.1.1 Dose Escalation Criteria

[redacted]

4.2 Start of Study and End of Study

The study period begins when the first participant signs the trial informed consent form (ICF) and ends when the last participant completes the follow-up visits, discontinues from the trial, or is lost to follow-up (i.e., the investigator is unable to contact the participant).

5 STUDY POPULATION

The study population includes adults with moderate-to-severe AD. Eligibility criteria include the following.

5.1 Inclusion Criteria

Participants must fulfil all of the following inclusion criteria for entry into the study:

1) Male or female aged ≥ 18 and < 75 years.

2) Able to participate and comply with all study procedures and restrictions, and willing to provide written informed consent to participate in the study.

3) Diagnosed with AD for [redacted], according to the American Academy of Dermatology Consensus diagnostic criteria (Eichenfield et al. 2014) at the Screening visit.

4) Moderate-to-severe AD, defined as:

a) EASI score ≥ 12 at the Screening visit and ≥ 16 at the Baseline visit

b) IGA ≥ 3 at the Screening visit and the Baseline visit

c) BSA ≥ 10% at the Screening visit and the Baseline visit

5) Documented history of inadequate response or lack of tolerability, as assessed by the investigator, to a stable regimen (≥ 4 weeks) of one or more topical treatment, e.g., TCS or TCI before the Screening visit, or for whom topical treatments are otherwise inadvisable.

6) Agree to apply a stable dose of a non-medicated emollient (moisturizer) twice daily at least one week before the Baseline visit and throughout the study.

7) Female participants who are not pregnant or breastfeeding and meet at least one of the following conditions:

a) Not of childbearing potential as described in Section 5.3.

b) Of childbearing potential and agrees to use a highly effective method of contraception as described in Section 5.3 consistently from signing of informed consent until 6 months after the last dose of study treatment. Contraception requirements do not apply to participants in an exclusively same-sex relationship. Female participants should not donate eggs until 6 months after the last dose of study treatment.

8) Male participants must be surgically sterilized (performed at least 6 months prior to Baseline [Day 1] visit and documented to no longer produce sperm); or from signing of informed consent until at least 6 months after the last dose of study treatment, agree to use highly effective methods of contraception as described in Section 5.3 with female partners of childbearing potential during the study and must also agree not to donate sperm during this period.

5.2 Exclusion Criteria

Participants fulfilling any of the following exclusion criteria are not eligible for entry into the study:

1) Severe cardiovascular, pulmonary, renal, autoimmune and metabolic illness(es), or any other acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into the study.

2) History of clinically significant abnormal laboratory values, as determined by the principal investigator (PI), including but not limited to the following:

a) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 × upper limit of normal (ULN) at the Screening visit.

b) Total bilirubin above 1.5 × ULN (unless the elevated bilirubin is related to confirmed Gilbert's Syndrome) at the Screening visit.

c) White blood cell count < 3,000/mm^3 (< 3.0 × 10^9/L) at the Screening visit.

Note: If the test results meet the above criteria, a repeat test may be performed to determine eligibility.

3) Positive hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) serology results at Screening visit as defined below:

   a) HBV: Positive test for hepatitis B surface antigen (HBsAg), OR positive test for hepatitis B core antibody (HBcAb) with negative test for hepatitis B surface antibody (HBsAb)

   b) HCV: Positive test for hepatitis C antibody

   c) HIV: Positive test for HIV antibody

4) Evidence of active or latent TB as confirmed by the screening TB test.

5) History of untreated or inadequately treated TB infection.

6) Active infection requiring treatment with systemic antibiotics, antivirals, antifungals, antiparasitics or antiprotozoals at the Screening and the Baseline (Day 1) visit.

7) Active unstable (e.g., in an acute flare) skin conditions in addition to AD that would interfere with the assessment of AD based on the investigator's clinical judgement.

8) Use of topical treatments such as TCSs, TCIs, topical phosphodiesterase-4 inhibitors and topical janus kinase (JAK) inhibitors for AD within 2 weeks before the Baseline (Day 1) visit.

9) Use of phototherapy for AD with ultraviolet (UV) A or UVB or regular use of a tanning booth within 4 weeks before the Baseline (Day 1) visit.

10) Use of 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.

11) Use of 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.

12) Receipt of a live (including live attenuated) vaccine within 2 months prior to the Baseline (Day 1) visit (participants must agree to avoid live [including live attenuated] vaccination during study treatment and within 3 months thereafter).

13) Any known hypersensitivity to any component of study treatment or other biologics (e.g., mAbs, fusion proteins)

14) Malignancy or a history of malignancy (exception: fully-treated skin basal cell or non-metastatic squamous cell carcinomas; or cervical carcinoma in situ with no evidence of recurrence within 5 years) prior to the Screening visit.

15) Planned major surgical procedure during the study.

16) Participation in another research study involving an investigational product within 3 months prior to the Baseline (Day 1) visit.

17) Women who are pregnant or nursing. All female participants with reproductive potential must have a negative pregnancy test prior to starting study treatment.

5.3 Contraception Recommendations

A female who is permanently surgically sterile or postmenopausal is not considered to be a female of childbearing potential and is not required to follow contraception recommendations.

Surgically sterile is defined as:

- Bilateral oophorectomy (surgical removal of both ovaries); or
- Bilateral salpingectomy (surgical removal of both fallopian tubes); or
- Hysterectomy (surgical removal of uterus)

Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.

A female who does not meet the definition of postmenopausal or permanently surgically sterile or is postmenarchal or pubertal but has not yet had menses is considered of childbearing potential and is required to practice at least one of the following highly effective methods of birth control consistently from signing of informed consent until 6 months after the last dose of study treatment.

- Combined (containing estrogen and a progestogen) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.
- Bilateral tubal occlusion/ligation.
- Vasectomized partner(s) provided that the vasectomized partner has received medical confirmation of the surgical success and is the sole sexual partner of the female trial participant of childbearing potential.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- True abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence

(e.g., using calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable.

The above-mentioned definition for true abstinence also applies to male participants. Contraception requirements do not apply to participants in an exclusively same-sex relationship.

5.4 Screen Failures

Screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention or enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

The participant who does not meet the criteria for participation in this study (screen failure) may be rescreened. A participant can only be rescreened once. If a participant fails screening for reason(s) which, in the opinion of the investigator, may be changed to make the participant eligible, the participant may be rescreened one time. In this case, the participant will re-sign the informed consent document and have all screening procedures performed. If a participant had a complete initial screening evaluation including TB test, the test will not be repeated for rescreening, provided the conditions noted in Section 5.1 and Section 5.2 of the protocol are met with no changes in the participant's medical history that warrant retesting, and no more than 90 days have passed. The investigators are encouraged to contact the medical monitor to confirm if subjects should or should not be rescreened.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Treatment Assignment

Cohort 1 will be an open label design. Approximately 15 consented participants who meet all eligibility criteria will be enrolled in Cohort 1 to receive three IV infusions of IMG-007 300 mg over 4 weeks. Participants will be assigned a unique enrollment number in ascending numerical order. Enrollment numbers are allocated sequentially in the order in which the participants are enrolled.

Cohort 2 will be a randomized, double-blind and placebo-controlled design. Approximately 40 consented participants who meet all eligibility criteria will be randomized at Baseline (Day 1) 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. Participants will be assigned a randomization number in ascending numerical order. The randomization number encodes the participant assignment to either IMG-007 [redacted] or matching placebo. Randomization will be performed using an interactive voice response system (IVRS) or interactive web response system (IWRS) software.

6.2 Treatment Blinding

Cohort 1 will be an open label design.

Cohort 2 will be a double-blind design. The study will be unblinded to select personnel from the Sponsor and/or participating CROs which will be specified in a separate document for the Blinding

Plan and Unblinding Process. The SRC team may receive unblinded data for safety evaluation. The study will remain blinded (except for emergency unblinding) for all other study personal/consultants, investigative site personnel, and study participants until the pre-specified unblinding to perform the primary analysis (Section 11.3.7). After the primary analysis, investigator, and study staff (except for emergency unblinding) as well as CRO staff (except for emergency unblinding) will remain blinded until the end of the study. To maintain the blind, all participants will receive three IV infusions over 4 weeks. Results from the PK and anti-drug antibody (ADA) measurements will not be communicated to the sites.

At initiation of the study, the study site will be instructed on the method of breaking the blind for individual participant in case of emergency. Blinding codes should only be broken for individual participants in emergency situations for reasons of participant's safety, or where knowledge of study treatment allocation will impact on the participant's medical management. The IVRS/IWRS will be used to provide the treatment assignment to the investigator. If unblinded, only the investigator and the affected participant will know the treatment assignment. Whenever possible, the investigator should inform the medical monitor when breaking the blind. When the blinding code is broken, the reason must be fully documented and entered in the case report form (CRF). In such cases, treatment with the investigational product must be stopped (Section 6.10.1.1) and the Medical Monitor must be contacted immediately to determine whether the participant should be withdrawn from study treatment.

6.3 Investigational Product Supply

IMG-007 and placebo will be supplied by the Sponsor and labeled appropriately as the investigational product for this study. The investigator must ensure that the investigational product will be used only in accordance with the protocol.

The investigational product administered in this clinical trial is IMG-007 protein provided as active substance (nominal 50 mg/mL) in a 2R Type I glass vial with a 13-mm rubber stopper integrated into a plastic cap. The IMG-007 vials are to be stored at 2 to 8°C and protected from light. The investigational product will be prepared for the desired dose and diluted with isotonic saline solution (0.9% sodium chloride marketed product) and to be administered via IV infusion.

The matching placebo of IMG-007 is identical in formulation to that of IMG-007 minus the active ingredient. The matching placebo is to be stored at 2 to 8°C and protected from light. The placebo will be prepared for the desired dose and diluted with isotonic saline solution (0.9% sodium chloride marketed product) and to be administered via IV infusion.

The isotonic saline solution (0.9% sodium chloride marketed product) to be used for dilution can be stored at room temperature.

For detailed instructions for storage, handling, reconstitution, and administration of all study treatments, please refer to the Investigational Medicinal Products Manual.

6.3.1 Packaging and Labeling

The labeling for IMG-007 and the matching placebo will be in accordance with Good Manufacturing Practice and Good Clinical Practice (GCP) and any other local regulatory requirements.

Each vial of IMG-007 or placebo will have a one-piece/booklet label attached to it and will be placed in a carton. The carton will have a one-piece/booklet label attached with the following information included: Sponsor name and address, protocol number, investigational product name, dosage form and strength (where applicable), amount of investigational product per container, lot/batch number, expiration date, medication identification number, storage conditions and any required caution statement(s) and/or regulatory statements, as applicable.

The investigational product for Cohort 1 and Cohort 2 will be packed and labeled separately. For Cohort 1, investigational product with open label for IMG-007 will be provided. For Cohort 2, investigational product with blinded label for IMG-007 or placebo will be provided. Additional information may be included on the label as applicable per local regulations. Both the vial label and the carton label will include a medication number.

6.3.2 Preparation and Dispensing

The investigational product will be prepared for the desired dose and diluted with isotonic saline solution (0.9% sodium chloride marketed product) to be administered via IV infusion.

Refer to the Investigational Medicinal Products Manual for details about preparation and dispensing of IMG-007 and placebo.

6.4 Dosing and Administration

IMG-007 should be administered via IV infusion.

Participants in Cohort 1 will receive IMG-007 300 mg on Day 1, Day 15, and Day 29.

Participants in Cohort 2 will receive IMG-007 [redacted] or matching placebo on Day 1, Day 15, and Day 29.

Participants will receive the study treatment at the study site. The investigational product will be diluted with normal saline and administered by continuous IV infusion over approximately 60 minutes at 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 during observation have resolved or stabilized, whichever is longer. Study sites should have access to equipment or facilities for the management of potential hypersensitivity reactions.

It is anticipated that the infusion should be completed within 4 hours after preparation of the infusion solution. Refer to the Investigational Medicinal Products Manual for details about dosing and administration of IMG-007 and placebo.

6.5 Dose Modifications and Delays

Dose modification of the study treatment is not allowed. Any inadvertent dose modifications should be discussed with the medical monitor. Dosing should occur as close as possible on the allocated visit day and within the visit windows specified in the SoA (Table 1), except that dosing may be interrupted due to reasons stated in Section 6.10.1.2. If a dose is not administered on schedule due to a visit occurring beyond the visit window specified in the SoA or dose interruption for reasons stated in Section 6.10.1.2, the dose may be administered if it is no later than 5 calendar days after the allocated

visit day (a 10-calendar day delay will be allowed for the last dose at Week 4) specified in the SoA. Otherwise, the dose will be considered missed, and dosing will resume with the next scheduled dose per the SoA.

6.6 Monitoring Potential Adverse Reactions to Treatment

The IB provides all the relevant information about the anticipated safety profile of IMG-007. New safety information will be provided through updates to the IB and suspected unexpected serious adverse reaction (SUSAR) reports provided to the investigators rather than by amendment to this section of the protocol. Key risks associated with the administration of IMG-007 including guidance for monitoring are summarized below.

There is limited clinical experience with IMG-007 to date. Potential safety risks of IMG-007 include injection/infusion site irritation, localized or systemic hypersensitivity reactions due to study treatment injection/infusion and potential immunogenicity, and infections.

Localized injection reactions may include pruritus, pain, erythema, swelling, rashes, or bleeding around the injection/infusion site. Systemic injection/infusion-related reactions may be immediate type (e.g., anaphylaxis, as defined in Sampson et al. 2006) or delayed type immune complex-associated hypersensitivity reactions (e.g., serum sickness). Symptoms of immediate type hypersensitivity reactions vary depending on severity, but may involve skin or mucous tissues (e.g., pruritus, flushing, hives, angioedema), gastrointestinal system (e.g., abdominal pain, vomiting), respiratory system (e.g., dyspnea, wheeze/bronchospasm, stridor), and cardiovascular system (e.g., hypotension, hypotonia, syncope). Severe systemic hypersensitivity reactions may require IV interventions. It is recommended that appropriate medical care to treat such reactions, including severe systemic reactions be readily available at the time of dosing. The investigator will decide whether required care can be provided at the clinic or whether transport to a hospital facility is warranted.

On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes. Participants should be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AEs observed during the observation 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.

Immune complex-associated hypersensitivity reactions (e.g., serum sickness) may occur several days or weeks after the study treatment infusion and may be manifested as fever, arthritis, pruritus, and rash requiring no or limited treatment, or in some cases, requiring IV interventions.

Participants must be permanently discontinued from study treatment if anaphylaxis (based on the criteria defined in Sampson et al. 2006) or other severe systemic hypersensitivity reactions (e.g., those with symptoms of respiratory and/or cardiovascular systems requiring IV interventions) occur. The medical monitor should be contacted as soon as feasible if study treatment is permanently discontinued in any participant due to these reasons.

Participants who permanently discontinue study treatment before the Week 4 visit should continue with all the remaining study visits.

6.7 Investigational Product Storage, Accountability, Return and Disposal

IMG-007 and placebo will be stored at a temperature between 2 and 8°C and protected from light.

Each dose of study treatment will be prepared individually in a restricted area on site/at the local hospital pharmacy by the site team member(s), according to the instructions provided in the Investigational Medicinal Products Manual. He/she will be a pharmacist or a study nurse, with documented appropriate qualifications and training, and authorized by the investigator according to local regulations. The material needed for study treatment preparation and administration will be supplied by the Sponsor. Sites could also use their own routine materials for some procedures.

The Sponsor (or designee) will review with the investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction, including responsibilities for the site versus the Sponsor (or designee). The investigational product should not be used for purposes other than as defined in the protocol. All the investigational drug products (IMG-007 and placebo) will be accounted for in accordance with GCP. There will be an investigational product accountability record with information for each participant and the investigator should maintain accurate records of the disposition of all investigational products received during the trial. These records should include the amounts and dates investigational product supplies were received, dispensed, administered, disposed and returned to the Sponsor. If temperature excursion or damage occurs to the investigational product supply shipments, the investigator should contact the clinical supply distribution vendor and the Site Monitor immediately. The Site Monitor will periodically check the supplies of the investigational product held by the investigator or pharmacist to verify accountability of all investigational product used.

The investigator will provide the investigational product only to the identified participants of this trial, according to the procedures described in this protocol. After the end of the trial, the Site Monitor will perform final accountability. Investigational product and all investigational product containers will be returned to the clinical supply distribution vendor or destroyed onsite according to the site's standard operating procedures, with documentation of destruction and/or shipment return. The CRO will verify the final report of drug accountability that is prepared and maintained in the investigator's Trial Master File.

It is the investigator's responsibility to ensure that participants are dosed correctly according to their assigned dosage regimen. The investigational product should be dispensed by the investigator, or by a qualified individual delegated by the investigator. An up-to-date treatment inventory/dispensation record must be maintained as described above. Records of the investigational product used and administered will be kept during the trial. Drug accountability will be noted by the Site Monitor during site visits and at the completion of the trial.

6.8 Study Intervention Compliance

Each investigator must judge whether the participants are able to follow the necessities of the clinical trial and to make regular visits to the clinical trial site. The investigator can exclude participants from clinical trial participation who will not follow medical instructions as judged by the investigator. Drug compliance is ensured by administration of the study treatment by authorized team member(s) at site.

6.9 Prior and Concomitant Therapy

The investigator must instruct the participants to notify the study site about any new medications they take after being enrolled into the study. All medications, procedures, and significant non-drug therapies (including physical therapy, chiropractic treatment, osteopathic manipulations, acupuncture, or blood transfusions) administered after the participant is enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies electronic case report form (eCRF). Each concomitant drug must be individually assessed against prohibited medication.

6.9.1 Permitted Concomitant Treatments (Medications and Therapies)

Concomitant medications permitted during the study include treatment with oral antihistamines, stable use of non-medicated emollients, over-the-counter supplements and vitamins, complementary or alternative medicine therapies (e.g., herbal products, supplements) and oral contraceptives. Other concomitant medications that a participant receives on a regular basis for chronic diseases may be continued if, in the opinion of the investigator, they do not put the participant at undue risk or interfere with the study evaluations. If there is a question regarding whether a concomitant medication may be used during the study, the study site should consult the study medical monitor.

6.9.2 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 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.

6.9.3 Rescue Therapy

It is recommended that the use of rescue medications be [redacted] if possible. Rescue medications will not be provided by the Sponsor.

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 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.

6.10 Early Withdrawal from Study

6.10.1 Discontinuation of Study Treatment

6.10.1.1 Permanent Discontinuation of Study Treatment

[redacted]

The medical monitor should be contacted as soon as feasible if study treatment is permanently discontinued in any participant due to the above reasons.

Other reasons for permanent discontinuation of study treatment include:

- Diagnosis of malignancy during the study, except for carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol

- Pregnancy
- Unblinding of study treatment for any reason in Cohort 2
- Participant failure to comply with protocol requirements or study-related procedure
- Participant receives systemic corticosteroids or non-steroidal immunosuppressive or immunomodulating medications (e.g., cyclosporin, methotrexate, azathioprine, mycophenolate-mofetil, JAK inhibitors, biologic agents, etc.)
- Participant receives a live (including live attenuated) vaccine
- Participant receives an investigational drug (other than IMG-007)
- Lack of efficacy/activity of the study treatment, defined as inadequate improvement in disease activity based on investigator's clinical judgment
- Physician decision
- Study is stopped by the Sponsor or health authority.

Note that discontinuation of study treatment does not represent withdrawal from the study. Participants who permanently discontinue study treatment before the Week 4 visit should continue with all the remaining study visits.

6.10.1.2 Temporary Discontinuation of Study Treatment

A participant who meets either of the below criteria will have the study treatment temporarily discontinued until laboratory abnormality recovers and/or event resolution.

- White blood cell count < 3,000/mm^3 (< 3.0×10^9/L) confirmed upon repeat testing.
- Any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or requiring oral medication(s) for longer than 2 weeks.

Note that a decision to restart the study treatment following any laboratory abnormality or infection described above will be made in consultation with the medical monitor.

6.10.2 Participant Withdrawal from the Study

In accordance with the Declaration of Helsinki and other applicable regulations, a participant has the right to withdraw from the study at any time at his/her own request or may be withdrawn at the discretion of the investigator for safety, compliance or administrative reasons.

A participant might withdraw from the study for any of the reasons below:

- Voluntary withdrawal of consent or study participation, at any time
- A participant's failure to comply with the protocol requirements or study-related procedures

- An intercurrent or safety event which, in the opinion of the investigator, requires the withdrawal of the participant

- Lost to follow-up

- Death

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 the study early after Week 12 should complete the Week 24 (Day 169)/EOS visit at withdrawal. All information, including the reason for early withdrawal will be recorded in the participant's study records and in the CRF.

For participants who are lost to follow-up or withdraw their consent to participate in the study, the procedures of withdrawal from the study will no longer apply.

6.10.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

6.11 Premature Termination or Temporary Suspension of the Study

The Sponsor reserves the right to terminate the study prematurely at any time for any reason at the sole discretion of the Sponsor. Any premature discontinuation will be appropriately documented according to local requirements (e.g., institutional review board [IRB]/ethics committee [EC], regulatory authorities, etc.).

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- For study termination:

    - Discontinuation of further study intervention development

- For site termination:
    - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
    - Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the independent ethics committee (IEC)/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/ IEC and/or regulatory authorities.

6.12 Study Stopping Rules

Study stopping rules are defined as follows. [redacted]

7 STUDY PROCEDURES AND ASSESSMENT

7.1 Study Procedures

7.1.1 Informed Consent Procedure

Informed consent must be obtained before a participant enters the trial and before any protocol-directed procedures are performed. The requirements of informed consent are described in Section 12.3.

7.1.2 Screening Period

Screening evaluations will be performed for all participants to determine study eligibility. These evaluations must be completed within 35 days prior to the first dose of study treatment. A screen failure is defined as a participant who has given informed consent and failed to meet the inclusion and or/exclusion criteria. Participants who fail to meet inclusion criteria or meet exclusion criteria can be rescreened once per investigator discretion. Each participant must be re-consented prior to each screening attempt.

If needed, eligible participants who have completed screening procedures but are not enrolled due to scheduling-related delays, site logistics, or Sponsor-imposed delays (e.g., due to protocol amendments or other), the screening window may be extended for up to three business days.

Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

Screening procedures and assessments performed at screening is specified in the SoA (see Table 1).

7.1.3 Treatment Period

Eligibility for disease activity must be confirmed at Baseline before any other assessment/procedure is performed.

Participants 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 in Cohort 2 will be randomized to receive three IV infusions of IMG-007 [redacted] or matching placebo administered 2 weeks apart at Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) in a blinded fashion. Participants will complete additional visits at Week 1 (Day 8), Week 6 (Day 43), Week 8 (Day 57) and Week 12 (Day 85)/EOT.

Study procedures and their timing are summarized in the SoA (Table 1). Assessments/procedures at a clinic visit should be performed in the following order:

1) Participant-reported outcomes

2) Investigator assessments (performed only by adequately trained investigators or sub-investigators; the same investigator or sub-investigator should perform all the evaluations for a given participant throughout the entire study period where feasible to minimize inter-assessor variability)

3) Safety and laboratory assessments

4) Administration of study treatment

Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.

Repeat or unscheduled samples may be taken for safety reasons at the discretion of the investigator or for technical issues with the samples.

In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternative strategies for the visits, assessments and monitoring may be implemented by the Sponsor or the investigator, as per local health authority/ethics requirements.

7.1.4 Follow-up Period

The participant must return to the study center for follow-up visits and complete the procedures for safety, PK, immunogenicity, and efficacy evaluations. The details for follow-up procedures are outlined in the SoA (Table 1).

7.1.5 End of Study

The EOS visit will be on Day 169.

The investigator may discontinue a participant's study participation at any time during the study when the participant meets the study treatment discontinuation criteria described in Section 6.10.1. A participant may discontinue his or her participation without giving a reason at any time during the study. Should a participant's participation be discontinued, the primary criterion for termination must be recorded by the investigator.

7.2 Safety Assessments

Safety assessments will include AEs, SAEs, vital signs and physical examination, 12-lead ECG, and laboratory assessments, including pregnancy tests.

Planned timepoints for all safety assessments are listed in the SoA (Table 1). Additional timepoints for safety tests (e.g., added as necessary per protocol needs) may be added during the study based on newly available data to ensure appropriate safety monitoring.

The investigator/designee will be responsible for determining the clinical significance of any results that fall outside of the laboratory normal ranges.

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, considering appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

7.2.1 Adverse Events Monitoring

The investigator and qualified designee(s) are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up the AE or SAE. Please see Section 8 for more details.

7.2.2 Laboratory Safety Assessments

Samples for hematology and blood chemistry (see Table 4) will be drawn at the timepoints as described in the SoA (Table 1) and analyzed at central laboratories. Further details of the procedures to be followed for sample collection, storage and shipment are detailed in the Laboratory Manual.

Table 4 Safety Laboratory Tests

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 for red cells, white cells, bacteria, casts, and crystals.

c) Serum 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.

Abbreviations: 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; TB = tuberculosis

7.2.3 Vital Signs and Physical Examination

Vital signs will be measured in semi-supine or supine position after at least 5 minutes of rest and will include respiratory rate, temperature, systolic and diastolic blood pressure, and pulse rate. Vital sign assessments can be repeated at the discretion of the PI or designee.

A complete physical examination will include, at a minimum, assessments of the skin, head and neck, cardiovascular, respiratory, gastrointestinal, and neurological systems. Please refer to the SoA (Table 1) as to when the assessments are required.

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.

7.2.4 12-Lead Electrocardiogram

The investigator or designee will perform ECG examinations at the timepoints listed in the SoA (Table 1).

Heart rate and PR, QRS, QT, and QTc intervals, etc., will be measured. Triplicate ECG will be taken if there are any clinically significant abnormalities detected by the physician in a single ECG.

Resting 12-lead ECGs should be recorded after the participant has been semi-supine or supine for a minimum of 5 minutes. ECGs will be interpreted on-site by the investigator to ensure participant safety. The PI (or designee) will evaluate ECG tracings to determine if they are normal, or if there are any clinically significant abnormalities. Site standard ranges will be used to determine if any parameters are considered out of range. ECGs can be repeated at the discretion of the PI or designee.

7.2.5 Pregnancy Testing

For female participant of childbearing potential, serum human chorionic gonadotropin (hCG) will be tested at the Screening, Baseline (Day 1), Week 2 (Day 15), Week 4 (Day 29) visits, and at selected follow-up visits. In addition, urine hCG test must be performed prior to each dosing visit. Following a negative pregnancy test result at Screening, appropriate contraception must be initiated or continued (for participant already on contraceptives) and maintained until 6 months after the last dose of study treatment.

Serum pregnancy tests will also be performed additionally whenever potential pregnancy is suspected. Additional pregnancy tests may also be undertaken if requested by the IEC or if required by local regulations. In the case of a positive confirmed pregnancy, the pregnancy will be immediately reported to the Sponsor and the participant will be followed up until completion or termination of the pregnancy (see Section 8.4).

7.3 Efficacy Assessments

To ensure consistency and reduce variability, the same evaluator should perform all investigator's assessments for a given participant throughout the study where feasible. Should it be necessary, another physician designated and trained by the investigator may conduct the above assessments in the investigator's absence.

7.3.1 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 the eCRF according to the completion guidelines.

The EASI will be assessed by the investigator at selected scheduled and unscheduled clinic visits. Further details on EASI will be provided in the Investigate Site File Binder.

7.3.2 Investigator 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. Further details on IGA will be provided in the Investigate Site File Binder.

7.3.3 SCORing Atopic Dermatitis (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. Assessments will be recorded in the eCRF.

The SCORAD will be assessed at selected scheduled clinic visits. Further details on SCORAD will be provided in the Investigate Site File Binder.

7.3.4 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. Further details on BSA will be provided as a component of SCORAD assessments in the Investigate Site File Binder.

7.3.5 Itch and Sleep Quality Numerical Rating Scale

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].

Further details on WI-NRS and SQ-NRS will be provided in the Investigate Site File Binder.

7.3.6 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".

Further details of assessments will be provided in the Investigate Site Files Binder.

7.3.7 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.

Further details of assessments will be provided in the Investigate Site File Binder.

7.3.8 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. Further details of DLQI will be provided in the Investigate Site Files Binder.

7.3.9 Atopic Dermatitis Lesion Photography

AD lesion photographs of a representative area of AD involvement which reflects the overall severity of disease (e.g., based on investigator's global assessment or SCORAD assessment) will be taken at Baseline (Day 1, pre-dose). Subsequent photographs of the same area will be taken at Week 12 (Day 85)/EOT and Week 24 (Day 169)/EOS. Additional photographs, especially those recording specific changes noted are also encouraged, if the participant is willing. AD lesion photography assessment is optional, but is encouraged, for participants in this study.

The photographs may be included in the clinical study report, regulatory submission documents, scientific publications, or in other public communications of clinical data to show changes in clinical presentations following treatment with IMG-007.

Instructions for taking the photographs are provided in the Photography Manual.

7.4 Pharmacokinetics and Immunogenicity Assessments

Blood will be collected to describe the IMG-007 PK and immunogenicity profiles as outlined in Table 5.

Participants with signs of any potential immune response to IMG-007 will be closely monitored with clinical evaluations. The PK and ADA samples may be collected at unscheduled visits for further evaluation.

Details concerning handling of PK and ADA serum samples, including labeling and shipping instructions, will be provided in the Laboratory Manual. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Samples will be shipped to the laboratory where samples will be analyzed for serum IMG-007 concentrations using a validated method.

Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study.

The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Bai et al. 2012; Rosenberg et al. 2004) to characterize ADA responses to IMG-007 in support of the clinical development program.

Table 5 PK and ADA Sampling Schema

Dose No.	Day	Pre-dose /Post-dose	PK blood sampling time	ADA sampling time	Sampling Window
1	1	Pre-dose	0 (pre-dose)	0 (pre-dose)	- 2 hours
	1	Post-dose	EOI	--	+10 mins
	8	Post-dose	7 days post-dose	--	± 3 days
2	15	Pre-dose	0 (pre-dose)	0 (pre-dose)	- 2 hours
	15	Post-dose	EOI	--	+10 mins
3	29	Pre-dose	0 (pre-dose)	0 (pre-dose)	- 2 hours
	29	Post-dose	EOI	--	+10 mins
	43	Post-dose	14 days post-dose	14 days post-dose	± 3 days
	57	Post-dose	28 days post-dose	28 days post-dose	± 3 days
	85/EOT	Post-dose	56 days post-dose	56 days post-dose	± 3 days
	113	Post-dose	84 days post-dose	84 days post-dose	± 3 days
	141	Post-dose	112 days post-dose	112 days post-dose	± 3 days
	169/EOS	Post-dose	140 days post-dose	140 days post-dose	± 3 days

Abbreviations: ADA = anti-drug antibody; EOI = end of Infusion; EOT = end of treatment; EOS = end of study; PK = pharmacokinetic

7.5 Pharmacodynamics Assessments

7.5.1 Circulating Biomarkers

Blood samples will be sampled for biomarker analysis.

Blood samples for analysis of receptor occupancy (RO) will be collected at Baseline (Day 1, pre-dose and end of infusion [EOI)], Week 1 (Day 8), Week 2 (Day 15, pre-dose and EOI), Week 4 (Day 29, pre-dose and EOI), Week 6 (Day 43), Week 8 (Day 57), Week 12 (Day 85)/EOT, Week 16 (Day 113), Week 20 (Day 141), and Week 24 (Day 169)/EOS.

Blood samples for analysis of inflammatory markers including TARC will be collected at Baseline (Day 1, pre-dose), Week 1 (Day 8), Week 2 (Day 15, pre-dose), Week 4 (Day 29, pre-dose), Week 6 (Day 43), Week 8 (Day 57), Week 12 (Day 85)/EOT, Week 16 (Day 113), Week 20 (Day 141), and Week 24 (Day 169)/EOS.

The sampling window for PD assessments of RO and inflammatory markers are as defined in Table 5. Details concerning the handling of blood samples, including labeling and shipping instructions are provided in the Laboratory Manual.

7.5.2 Atopic Dermatitis Lesion Biopsy

AD lesion biopsy is optional, but is encouraged, for participants in this study. At Screening, participants who are willing to provide skin biopsies will indicate their consent for biopsy in the ICF. Skin biopsy samples from lesional skin will be collected at the Baseline (Day 1, pre-dose), Week 12 (Day 85)/EOT, and Week 24 (Day 169)/EOS visits. The biopsy should be sampled under instructions outlined in the Laboratory Manual.

Skin biopsies will be analyzed for transcriptome sequencing, immunohistochemical staining for skin thickness, keratin (K)16, OX40, and OX40L.

8 COLLECTION OF ADVERSE EVENTS AND SAFETY REPORTING

The PI should make sure that all the staff involved in the study are familiar with the content of this section.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up.

The term AE is used to include both serious and non-serious AEs if not specified.

8.1 Definitions

8.1.1 Adverse Event

An AE is the development of any untoward medical occurrence in a patient 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 (see Section 8.2.3).

8.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- **Results in death**

  Death is the outcome and therefore always record the medical condition that results in the fatal outcome as the SAE term.

  Deaths with an unknown cause should be reported as SAE "death with unknown cause". Every attempt should be tried to obtain the cause of death. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the autopsy report should be forwarded to the Sponsor.

- **Is immediately life threatening**

  The term "life threatening" in the definition of seriousness refers to an event in which the participant 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.

- **Requires in-patient hospitalization or prolongation of existing hospitalization**

  In general, hospitalization signifies that the participant has been admitted (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.

  The following situations are NOT considered as hospitalizations or prolongation of existing hospitalization that meet SAE criteria:

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline;

- Protocol specified admission. Routine clinical management for mild to moderate laboratory tests abnormality at scheduled visits will not be regarded as leading to prolonged hospital stay and should be reported as non-serious AE according to the definition of AE;

- Hospitalizations are within the local medical practice for medical insurance purpose while the disease treated would normally be an outpatient practice (e.g., hospitalization for a common cold as local medical insurance can cover).

All pre-planned hospitalizations need to be documented in the participant records at Baseline. All hospitalization during the study should be documented with a clear statement indicating that this hospitalization fulfills the SAE exemption specified in the protocol.

- **Results in persistent or significant disability or incapacity**

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- **Is a congenital abnormality or birth defect**

  This is applicable to any congenital anomaly/birth defect in a neonate born to a female participant exposed to study treatment, or the female partner of a male participant exposed to study treatment. See more information in Section 8.4.

- **Is an important medical event** that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of seriousness. These should usually be considered as serious.

All SAEs will be reported to the Sponsor or designee within 24 hours by the investigator after being aware of. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available. Please see more information in Section 8.3.

8.1.3 Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)

- The date when the AE started and stopped

- The maximum severity reported or changes in severity (report only the maximum severity for a calendar day). See Section 8.1.4 for severity assessment.

- Whether the AE is serious or not

- Investigator causality rating against the study treatment (yes or no). See Section 8.1.5 for causality assessment.
- Action taken with regard to study treatment
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs, either on the eCRF or SAE reporting form:

- Date the AE meeting the criteria for SAE (SAE onset date)
- Date the investigator becoming aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of the SAE

8.1.4 Severity Assessment

For all AEs, severity should be assessed using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, published on 27 November 2017, which provides a grading severity scale for each AE term within a system organ class based on the following general guideline:

- **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 (ADL)*.
- **Grade 3** Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

- **Grade 4** Life-threatening consequences; urgent intervention indicated.

- **Grade 5** Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The severity grade as listed by AE term and system organ class in the NCI CTCAE Version 5.0 should be used to define the severity for each AE observed.
(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

8.1.5 Causality Assessment

The investigator will assess and document the causal relationship between the study treatment and each AE by answering the question "Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?"

A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.

An answer of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

An assessment of "no" indicates that there is non-plausibility or the existence of a clear alternative explanation.

Factors to be considered in assessing the reasonable possibility of a relationship of the AE to study treatment include:

- Time Course. Exposure to study treatment. Has the participant actually received the investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the study treatment?

- Consistency with the known drug profile. Was the AE consistent with the previous knowledge of the investigational product (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the study treatment?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.

- Re-challenge experience. Did the AE reoccur if the study treatment was reintroduced after having been stopped? (Note: The Sponsor would not normally recommend or support a re-challenge.)

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

- In difficult cases, other factors could be considered such as: Is this a recognized feature of overdose of the investigational product? Is there a known mechanism?

SAEs will be reviewed by the Sponsor medical monitors and physicians, and further queries will be issued if necessary. The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator. The causality assessment given by the investigator should not be downgraded by the Sponsor. If the Sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the Sponsor should be provided with the report.

8.2 Method of Detecting and Collecting Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF.

8.2.1 Time Period and Frequency for Collecting Adverse Events

The follow-up period is defined as up to Day 169/EOS. All AEs/SAEs will be collected from the time the participant signs the ICF. After the follow-up period, any SAE that is related to study treatment by investigator assessment should be reported directly to the Sponsor's pharmacovigilance team.

8.2.2 Follow-up of Adverse Events

After the initial AE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Any AE that is unresolved at the participant's last study visit will be followed by the investigator for as long as medically indicated (this may be beyond the follow-up period), but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with any ongoing AEs at the end of the study, if judged necessary.

8.2.3 Adverse Events Based on Laboratory Test and Examination

Safety assessments, including protocol mandatory laboratory tests, ECG, vital signs, and physical examination, as specified in Section 7.2, will be collected and summarized in the clinical study report by worsening shift change from the baseline value. With this objective way of safety analysis, AE reporting based on examinations and laboratory tests by the investigator should well consider the baseline value and the dynamic changes over time.

8.2.3.1 Laboratory Abnormality

A laboratory test result (including vital signs, ECG, etc.) must be reported as an AE if it meets any of the following criteria:

- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)
- Leads to medical intervention (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings and to document his/her assessment for abnormal laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. The AEs relevant to abnormal laboratory values should be followed up till resolution, stabilization (e.g., to baseline value) or an explanation is available, or the participant is lost to follow-up.

Abnormality of a laboratory value, which is unequivocally due to natural disease progression, should not be reported as an AE.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

8.2.3.2 Physical examination

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the Baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3 Expedited Safety Reporting

Investigators must fill the SAE report form and other safety report form (e.g., pregnancy report) provided by the Sponsor and report these events to the pharmacovigilance safety database of the Sponsor immediately (within 24 hours of becoming aware of the event), regardless of relationship to the study treatment.

The investigator will submit any updated SAE information to the Sponsor within 24 hours of it being available. For fatal or life-threatening SAEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel are required to respond urgent queries immediately but no later than 24 hours of when he or she receives the queries.

Training of SAE reporting will be provided by the Sponsor for each study.

The Sponsor assumes responsibility for expedited reporting of SUSARs to the regulatory authorities and the EudraVigilance database. The Sponsor will also report all SUSARs to the investigator and the head of the investigational institute where required. The investigator (or Sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.4 Pregnancy Report

All pregnancy events must be reported in the period starting from the first dose until 6 months after the last dose of study treatment. The pregnancy itself is not considered to be an AE or SAE, while if the pregnancy outcome meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs as specified in Section 8.3.

If a female participant becomes pregnant during the study, the investigator must report the pregnancy to the Sponsor within 24 hours of awareness using the Pregnancy Report/Follow-up Form, and to the relevant institutions in a timely manner per local requirement.

The investigator should follow up on the pregnancy outcome (e.g., any early termination of pregnancy, or a live birth) until 4 weeks after delivery and notify the Sponsor and the EC (or other organizations as required by local regulations) of the pregnancy outcome.

If a male participant's partner becomes pregnant during the clinical study, the investigator must report the pregnancy to the Sponsor within 24 hours of learning of the pregnancy and submit the completed Pregnancy Report/Follow-Up Form. Consent should be obtained from the male participant's partner prior to obtaining any pregnancy result and outcome.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the pharmacovigilance team of the Sponsor.

9 SAFETY MONITORING

9.1 Safety Review Committee

A SRC consisting of three independent physicians will be convened to review safety data, dose escalation criteria, and the study stopping criteria. [redacted] The medical monitors from the CRO and the Sponsor will confirm and document in the study file the dose escalation decision before dosing in the subsequent cohort can proceed. The SRC membership, roles and responsibilities, meeting schedules, communication plans, and other details will be documented in the SRC Charter.

Recommendations by the SRC will be shared with the investigators.

10 DATA MANAGEMENT

The investigators are responsible for the accuracy, compliance to the protocol, completeness, and legibility of data documented in the eCRF and in the source documents. All data will be entered by the investigators or authorized trial team members at the site using a validated remote electronic data capture (EDC) system. The EDC system complies with all relevant regulations of the United States Food and Drug Administration, with Part 11 of Title 21 of the Code of Federal Regulations (21 CFR Part 11: Electronic records; Electronic signatures), and other local regulations, if applicable. Discrepancy in the data will be brought to the attention of the clinical team and the investigational site personnel, if necessary. Resolution of these issues will be reflected in the database. Data management details will be outlined in a separate data management plan.

All aspects of the study will be carefully monitored by the Sponsor or its authorized representatives for compliance and applicable regulations with respect to the current GCP and standard operating procedures.

The Sponsor ensures that appropriate monitoring procedures are performed throughout the study. During monitoring visits, the facilities, investigational product storage area, CRFs, participant's source documents, and all other study documentation will be inspected/reviewed by the Sponsor representative in accordance with the Study Monitoring Plan. Accuracy will be checked by performing source data verification or source data review, comparing entries made into the CRFs against appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be documented in the Study Monitoring Plan.

11 STATISTICAL CONSIDERATIONS

11.1 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]

11.2 Analysis Sets

- Safety analysis set will be used for safety analyses, which will include 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 also be used for demographic and baseline characteristics.

- Modified full analysis set will be used for efficacy analyses, which will include 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.

- PK analysis set will include 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.

- Immunogenicity analysis set will include 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.

- PD analysis set will be used for PD analyses, which will include 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.

11.3 Statistical Analysis

Unless otherwise stated, all data analysis will be reported under the respective treatment groups (placebo, IMG-007 300 mg, and IMG-007 [redacted]). In addition, as a sensitivity analysis, data for the combined active groups of IMG-007 300 mg and [redacted] will also be reported in the tables/figures. Nominal two-sided significance level of 0.05 will be used for all comparisons for which p-values are generated. Also, 95% confidence intervals will be used, wherever reported.

11.3.1 Analysis of Safety

Safety variables including incidence and severity, and duration of TEAEs and changes from baseline of relevant parameters (such as vital signs, ECGs, and clinical laboratory values) will be summarized.

- AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version currently in use by the Sponsor at the time of database lock). TEAEs are defined as events started after initiation of the first dose of study treatment or events present that worsen after the start of dosing. The number and proportion of participants experiencing one or more TEAEs will be summarized by severity, and relationship to study treatment.

- Prior and concomitant medications (including rescue medications) will be coded using the World Health Organization Drug Dictionary (WHODrug). The number and proportion of participants taking prior and/or concomitant medications will be summarized.

- Vital sign (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature) and ECG parameters will be summarized by visit descriptively. Changes from baseline, number, and proportion of participants with clinically important values will be presented descriptively.

- Clinical laboratory parameters will be summarized using descriptive statistics, by changes from baseline, post-dosing shift from Baseline (Day 1) in the normal or abnormal category of laboratory values by visit, and number and proportion of participants with a treatment-emergent clinically significant abnormal value based on predefined criteria, and data listings.

11.3.2 Analysis of Pharmacokinetics

Serum concentration data will be tabulated and summarized (geometric mean, arithmetic mean, minimum, maximum, SD and % coefficient of variation) by treatment group for each visit at which samples were taken.

It is intended that data from this study will be combined with data from other studies to better characterize the PK of IMG-007, as well as to explore the relationship between exposure and

efficacy, which will be provided in a population PK/PD analysis plan. The results of these analyses will be described in a separate population PK/PD report.

11.3.3 Analysis of Efficacy Endpoints

Continuous efficacy variables will be summarized using descriptive statistics which will include mean, median, minimum, maximum, Q1 and Q3, standard error and standard deviation. Categorical efficacy variables will be summarized by frequency and percentage for each category.

While the primary comparison of interest for efficacy endpoints will be within Cohort 2, for IMG-007 [redacted] versus placebo group, a broader comparison including 300 mg group versus placebo and the combined 300 mg and [redacted] versus placebo are also of additional, exploratory interest. For analysis within Cohort 1 (i.e., 300 mg group), efficacy comparison with baseline at each visit will be performed based on difference relative to zero. All analysis will use nominal two-sided significance level of 0.05.

For continuous efficacy endpoints, a mixed-effect model with repeated measures (MMRM) will be used. This model includes visit as a factor and respective baseline score as covariate for both Cohorts 1 & 2, and additionally treatment and treatment-by-visit interaction as factors for Cohort 2 only. [redacted]

Sensitivity analysis using other missing data handling approaches will also be performed. Further details including handling of specific intercurrent events and missing data imputations will be specified in the prospective statistical analysis plan (SAP).

11.3.4 Analysis of Immunogenicity

Samples to assess anti-IMG-007 antibodies will be collected for all participants and in sites that are able to adequately perform sampling, handling, and processing procedures outlined in the Laboratory Manual.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of participants who develop detectable ADA. The incidence of positive ADA will be reported for evaluable participants.

11.3.5 Analysis of Pharmacodynamics Endpoints

Biomarker data will be listed by participant and visit/timepoint. Additional analyses may be conducted as appropriate.

Skin punch biopsy data will be listed and summarized by visit.

11.3.6 Analysis of Exploratory and Other Endpoints

Analyses of exploratory endpoints listed in Section 3 will be generally similar to the primary and secondary analyses, which will be detailed in the SAP.

11.3.7 Timing of Analyses

[redacted]

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory and Ethical Considerations

Before initiating a trial/study, the investigator/institution must have written and dated approval/favorable opinion from the IRB/IEC for the study protocol/amendment(s), written ICF, any consent form updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects. The IRB/IEC approval must identify the protocol version as well as the documents reviewed.

This study will be conducted in compliance with International Council for Harmonization (ICH) GCP Guidelines, Declaration of Helsinki (Seoul 2008), Regulation (EU) No 536/2014, and in accordance with applicable national, state and local laws of the pertinent regulatory authorities.

The Sponsor and investigators must not amend this study protocol unilaterally without mutual agreement. The amended protocol cannot be conducted until it is approved by the IRB/IEC. When investigators have to change or deviate from the study protocol to eliminate the direct and immediate hazards to subjects, they must notify the IRB/IEC and Sponsor in writing to explain and record all the deviations as soon as possible.

During the clinical study, any amendment made to the study protocol should be submitted to the IRB/IEC, and corresponding amendment to other documents can also be made, when necessary, then be submitted and/or approved as required by the EC. Investigators are responsible for data protection.

12.2 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, recruiting materials and all the subject materials will be submitted to the IRB/IEC for review and approval. The subjects can be enrolled only after the approval of the protocol and ICF. Amendment to the protocol can only be implemented after it is reviewed and approved by the IRB/IEC.

It will be decided by the IRB/IEC whether the subjects who have signed the previous version of ICF should re-sign a new version.

12.3 Informed Consent Process

The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the participant's entry into the study and of the informed consent process should be recorded in the participant's source documents including the date. The original ICF signed and dated by the participant and the person consenting the participant prior to the participant's entry into the study, must be maintained in the investigator's study file and a copy given to the participant. In addition, if a protocol is amended and it impacts the content of the informed consent, the ICF must be revised. Participants participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the participant and the person consenting the participant must be maintained in the investigator's study files and a copy given to the participant.

12.4 Confidentiality of Participant's Information

Subject confidentiality and privacy are strictly held in trust by the investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the EC, regulatory agencies or the pharmaceutical company supplying the investigational product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the EC, regulations, or Sponsor requirements.

The conduct of this study and the processing of any personal data collected from each participant (or from a participant's healthcare professional or other relevant third-party sources) by the Sponsor or its designee, the site and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation (GDPR) EU 2016/679. The Sponsor or its designee shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions including passwords and security control measures to protect study-specific data, both in paper and electronic format.

The investigators shall provide coded data to the Sponsor or its designee, which does not reveal the participant's name, full date of birth, or any other information which can identify the participant. All personal information shall be replaced with a Subject Identification Code (SID) code before any information leaves the investigator sites.

The investigator shall report any data breaches that might occur to the Sponsor or its designee, without undue delay. The Sponsor has implemented a Business Practice to address Data Breaches that complies with the requirements of applicable laws and regulations including the GDPR. The Data Breach procedures in the Business Practice provide specific responses to actual or potential threats and involve investigation, containment and mitigation. If applicable, the authorities and the data subjects shall be notified of a data breach, within the required timeframes of the applicable laws and regulations, including those of the GDPR.

12.5 Quality Assurance and Quality Control

The Sponsor or its representative may conduct audits of clinical research activities to evaluate compliance with GCP guidelines and regulations. The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study participating for audits and/or inspections. If the investigator is contacted by any regulatory authorities regarding an inspection, he/she should contact the Sponsor/CRO immediately. He/she must cooperate fully and make every effort to be available for audits and or inspections.

The Sponsor oversees ensures that appropriate monitoring procedures are performed before, during and after the study. Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of participant rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities. Monitoring will include on-site and remote visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject source documents, and all other study documentation will be inspected/reviewed by the Sponsor or Sponsor representative in accordance with the Monitoring Plan.

12.6 Data Handling and Record Keeping

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained.

Essential documents must be retained by the investigator according to the period of time outlined in the clinical trial agreement. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all participants;
- Participant identification code list, screening log (if applicable), and enrollment log;
- Record of all communications with the investigator and the IRB/EC;

- Composition of the IRB/EC;
- Record of all communications between the investigator, Sponsor, and their authorized representative(s);
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Study treatment accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (participant record, hospital records, laboratory records, etc.);
- All other documents listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The investigator must notify the Sponsor if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The investigator must obtain approval in writing from the Sponsor prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by health authorities. The investigator or institution should take measures to prevent accidental or premature destruction of these documents.

12.7 Publication Policy

All protocol- and amendment-related information, with the exception of the information provided by the Sponsor on public registry websites, is considered the Sponsor's confidential information and is not to be used in any publications. Only information that is previously disclosed by the Sponsor on a public registry website may be freely disclosed by the investigator or its institution, or as outlined in the Clinical Trial Agreement. Information related to the study protocol, amendment and IB is not to be made publicly available (e.g., on the investigator's or their institution's website) without written approval from the Sponsor. Information proposed for posting on the investigator's or their institution's website must be submitted to the Sponsor for review and approval.

This allows the Sponsor to protect proprietary information and to provide comments.

Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Results will be uploaded to the clinical trials information system (CTIS) database within one year after end of trial in accordance with CTR Annex IV.

12.8 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of the Sponsor's information. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all participants who sign an ICF and are screened for entry into the study. Participants who fail screening must have the reason(s) recorded in the participant's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to participant records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

At the time results of this study are made available to the public, the Sponsor will provide investigators with a summary of the results that is written for laypersons. The investigator is responsible for sharing these results with the participant and/or their caregiver as agreed by the participant.

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14 APPENDICES

14.1 APPENDIX 1: Tuberculosis Risk Assessment

14.2 APPENDIX 2: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue or uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch or flush, swollen lips, tongue or uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that participant (minutes to several hours):

   a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure*

   b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*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× 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years

Reference: Sampson et al. 2006

14.3 APPENDIX 3: Prior Protocol Amendments

14.3.1 Summary of protocol changes in Amendment 1, Version 2.0:

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

14.3.2 Summary of protocol changes in Amendment 2, Version 3.0:

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted].

14.3.3 Summary of protocol changes in Amendment 3, Version 4.0:

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

14.3.4 Summary of protocol changes in Amendment 4, Version 5.0:

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

14.3.5 Summary of protocol changes in Amendment 5, Version 6.0:

Section Number and Section Name	Description of Change	Brief Rationale for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]