Clinical Study Protocol

A Phase 1b/2a Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of IMG-007 in Adult Alopecia Areata Participants with 50% or Greater Scalp Hair Loss

Investigational Product:	IMG-007
Protocol Number:	IMG-007-202
Protocol Version:	Version 4.0
Version Release Date:	02 August 2024
Development Phase:	1b/2a
Sponsor:	Inmagene LLC
Sponsor Address:	12526 High Bluff Drive, Suite 345, San Diego CA, 92130, USA
IND Number:	164,904

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 investigator site files.

Report serious adverse events (SAEs) within 24 hours on the SAE form provided in the investigator site files via email/fax.

SPONSOR SIGNATORY

Protocol Version: 4.0
Protocol Date: 02 August 2024

[redacted]
Inmagene LLC

Date

INVESTIGATOR

I have read and agree to the protocol IMG-007-202 titled "A Phase 1b/2a Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of IMG-007 in Adult Alopecia Areata Participants with 50% or Greater Scalp Hair Loss" Version 4.0, 02 August 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.

Clinical Site:

Location:

Investigator:

Print Name	Title
Signature	Date

PROTOCOL AMENDMENT DETAILS

History of Amendments

[redacted]

Summary of changes in the current amendment:

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

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LIST OF ABBREVIATIONS

Term	Definition
AA	Alopecia Areata
AAPPO	Alopecia Areata Patient Priority Outcome
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
AT	Alopecia Totalis
AU	Alopecia Universalis
AUC	Area Under the Concentration-time Curve
$AUC_{\tau,SS}$	Area Under the Concentration-time Curve from Time 0 to τ (the Dosing Interval) at Steady State
CL	Central Compartment Clearance
C_{max}	Peak Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Event
DPCP	Diphenylcyclopropenone
EC	Ethics Committee
EC_{90}	90% Maximal Effective Concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
HBcAb	antibody to 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
HIV	Human Immunodeficiency Virus

Term	Definition
HMG-CoA	Hydroxymethylglutaryl Coenzyme A
IA	Interim Analysis
IATS	Investigator's Assessment of a Target Scalp Lesion
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IGA-EB	Investigator's Global Assessment of Eyebrows
IGA-EL	Investigator's Global Assessment of Eyelashes
IGA-FN	Investigator's Global Assessment of Fingernails
IL	Interleukin
IRB	Institutional Review Board
IV	Intravenous
JAK	Janus Kinase
mAb	Monoclonal Antibody
MMF	Mycophenolate Mofetil
MMRM	Mixed Model Repeated Measure
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect Level
OX40L	OX40 Ligand
PD	Pharmacodynamics
PGIC	Patient Global Impression of Change
PGIC-AA	Patient Global Impression of Change of Overall Alopecia Areata
PGIC-EB	Patient Global Impression of Change of Alopecia Areata on the Eyebrows
PGIC-EL	Patient Global Impression of Change of Alopecia Areata on the Eyelashes
PGIC-FN	Patient Global Impression of Change of Alopecia Areata on the Fingernails
PGIC-S	Patient Global Impression of Change of Alopecia Areata on the Scalp
PGIS	Patient Global Impression of Severity
PGIS-AA	Patient Global Impression of Severity of Overall Alopecia Areata
PGIS-EB	Patient Global Impression of Severity of Alopecia Areata on the Eyebrows
PGIS-EL	Patient Global Impression of Severity of Alopecia Areata on the Eyelashes
PGIS-FN	Patient Global Impression of Severity of Alopecia Areata on the Fingernails
PGIS-S	Patient Global Impression of Severity of Alopecia Areata on the Scalp
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious Adverse Event

Term	Definition
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½\ el}$	Terminal Elimination Half-Life
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Event
Th	T-helper
ULN	Upper Limit of Normal
US	United States
UV	Ultraviolet
Vc	Central Compartment Volume

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: Inmagene LLC	**Protocol Number:** IMG-007-202
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:** 02 August 2024
Protocol Title: A Phase 1b/2a Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of IMG-007 in Adult Alopecia Areata Participants with 50% or Greater Scalp Hair Loss	
Number of Participants: Approximately 30 participants	
Study Centers: Multicenter	

Study Objectives:

Primary Objective

- To evaluate adverse events (AEs) emergent from multiple doses of IMG-007 in adult participants with alopecia areata (AA)

Secondary Objectives

- To evaluate the efficacy of multiple doses of IMG-007 in AA participants as measured by Severity of Alopecia Tool (SALT) at Week24

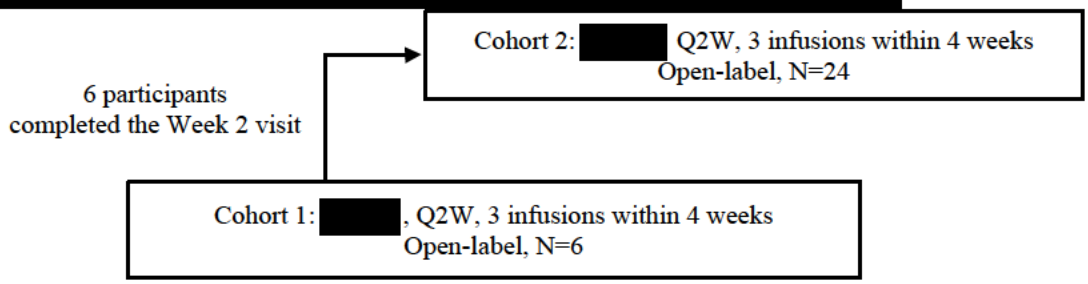
Exploratory Objectives

- To further evaluate the efficacy of multiple doses of IMG-007 in AA participants as measured by SALT and other investigator's assessments and patient reported outcomes
- [redacted]

Study Design:

This is a phase 1b/2a, open label, dose escalation study to assess the safety, PK, efficacy, and PD of IMG-007 in AA participants. Approximately 30 participants will be enrolled. The study will consist of two dose cohorts to be initiated sequentially in ascending dose order: Cohort 1 with six participants receiving three IV infusions of IMG-007 [redacted] over 4 weeks and Cohort 2 with 24 participants receiving three IV infusions of IMG-007 [redacted] over 4 weeks.

[redacted]



Each dose cohort will consist of four periods: a screening period of up to 5 weeks, a 16-week treatment period, an 8-week follow-up period, and a 12-week extended follow-up period post end of study (EOS).

- **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 113 (16 weeks): Participants who meet all eligibility criteria will be enrolled and will receive three IV infusions of IMG-007 [redacted] or [redacted] administered 2 weeks apart at the Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) visits. The study site will contact participants by telephone approximately 24 hours after each infusion for assessment of AEs and/or concomitant medications.

  On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes with a slower rate during the first 15 minutes. Participants will be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AEs observed 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 should be analyzed by a local laboratory if feasible. Study sites should have access to equipment or facilities for the management of potential hypersensitivity reactions.

  In addition to dosing visits, participants will also complete visits at Week 1 (Day 8), Week 6 (Day 43), Week 8 (Day 57), Week 12 (Day 85) and Week 16 (Day 113)/end of treatment (EOT).
- **Follow-up Period**: Day 113 to Day 169 (8 weeks): The follow-up period consists of two visits: Week 20 (Day 141) and end of study (EOS; Week 24 [Day 169]) visits.
- **Extended Follow-up Period Post EOS:** Day 169 to 253 (12 weeks): The extended follow-up period after EOS consists of two visits: Week 30 (Day 211) and Week 36 (Day 253).

Participants who discontinue 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 16 visit should complete the Week 16 (Day 113)/EOT visit at withdrawal.

Participants who withdraw from study early during the follow-up period should complete the Week 24 (Day 169)/EOS visit at withdrawal.

Participants who discontinue early after Week 24/EOS visit but before the Week 36 visit should complete Week 36 (Day 253) visit at withdrawal.

A participant who withdraws from the study prior to receiving two doses of study treatment (i.e., completing the Week 2 visit) for reasons other than AEs will be replaced.

Safety Monitoring and Dose Escalation:

A safety review committee (SRC) consisting of three independent physicians will convene 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

Treatment should be permanently discontinued if individual participants experience the following:

- Any anaphylaxis (based on criteria defined in Sampson et al 2006) within 24 hours of dosing that is judged by the investigator to be potentially related to study treatment
- Any Grade 3 or higher AE that is judged by the investigator to be clearly related to study treatment (i.e., without a clear alternative etiology)
- Any serious AE (SAE) that is judged by the investigator to be clearly related to study treatment (i.e., without a clear alternative etiology)
- Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN) and/or aspartate aminotransferase (AST) > 3 × ULN with a total bilirubin > 2 × ULN (unless the elevated bilirubin is related to Gilbert's Syndrome) confirmed upon repeat testing.

Other reasons for permanent discontinuation of study treatment are detailed in the protocol.

Dose Escalation Criteria

[redacted]

Study Stopping Criteria

[redacted]

Study Population:

The study population includes adults with AA. Eligibility criteria include the following:

Inclusion Criteria

1) Male or female aged ≥ 18 and ≤ 65 years when signing the consent form.
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) Clinical diagnosis of AA with current episode of hair loss of [redacted] prior to the Screening visit.
4) No evidence of terminal hair regrowth within [redacted] prior to the Screening and Baseline (Day 1) visits.
5) AA with ≥ 50% scalp involvement as defined as SALT score ≥ 50 (of total 100), including AT and AU, at the Screening and Baseline (Day 1) visits.

   Note: Recruitment of participants with AT or AU will be limited to no more than 10% (i.e., up to one participant in Cohort 1 and up to two participants in Cohort 2).
6) 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.
7) Male participants must agree to practice true abstinence; 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 with female partners of childbearing potential and must also agree not to donate sperm.

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:
   - ALT or AST ≥ 2.5 × ULN at the Screening visit.
   - Total bilirubin above 1.5 × ULN (unless the elevated bilirubin is related to confirmed Gilbert's Syndrome) at the Screening visit.
   - 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 exclusion 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:
   - 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)
   - HCV: Positive test for hepatitis C antibody
   - HIV: Positive test for HIV antibody
4) Evidence of active or latent tuberculosis (TB) as confirmed by the screening TB test at the Screening visit.
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 Baseline (Day 1) visit.
7) Concurrent hair loss due to other etiologies including but not limited to androgenetic alopecia (only exclude Ludwig Type ≥ II for female pattern or Norwood-Hamilton Stage ≥ IV for male pattern), traction and scarring alopecia, trichotillomania, telogen effluvium, and drug-induced hair loss.
8) Primary "diffuse" type of AA.
9) Active inflammatory diseases on the scalp (e.g., tinea capitis, scalp psoriasis, seborrheic dermatitis) that would interfere with the assessment of AA based on the investigator's clinical judgement.
10) History or presence of hair transplants or micropigmentation of the scalp.

    Note: microblading of the eyebrows is permitted.
11) Active systemic diseases that may cause hair loss (e.g., thyroiditis, systemic lupus erythematosus, iron deficiency).
12) Use of topical treatments for AA within 2 weeks before the Baseline (Day 1) visit, such as corticosteroids, calcineurin inhibitors, JAK inhibitors (e.g., ruxolitinib), antimicrobials, anthralin, diphenylcyclopropenone (DPCP), squaric acid, minoxidil or any other medication which, in the opinion of the investigator, may affect hair regrowth.

    Note: Topical treatments are permitted outside of the scalp, eyebrows and eyelashes.
13) Use of non-biologic systemic (oral or injectable) agents including conventional immunosuppressants or immunomodulators (e.g., corticosteroids, dapsone, methotrexate, mycophenolate mofetil, cyclosporine A, azathioprine, hydroxychloroquine, sulfasalazine, and other approved drugs) within 4 weeks or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit.
14) Use of oral JAK inhibitors within 8 weeks prior to the Baseline (Day 1) visit.

    Note: Recruitment of participants with a history of inadequate response (defined as failure to achieve ≥ 50% improvement in hair loss [equivalent to ≥ 50% improvement in SALT score] after approximately 6 months of treatment) to an oral JAK inhibitor will be limited to no more than 20% (i.e., up to one participant in Cohort 1 and up to five participants in Cohort 2).
15) Use of oral or injectable agents (minoxidil, apremilast, finasteride, hydroxymethylglutaryl-CoA reductase inhibitors [statins], herbal medicines) for the treatment of AA within 4 weeks prior to the Baseline (Day 1) visit.
16) Use of biologic therapy (e.g., mAbs against interleukin [IL]-17, IL-4, and IL-13 or other investigational products) or platelet-rich plasma within 3 months or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit.

17) Use of phototherapy for the treatment of AA with ultraviolet (UV) A or UVB or any other type of light therapy that, in the opinion of the investigator, may affect hair regrowth within 4 weeks before the Baseline (Day 1) visit.
18) Receipt of a live, including live attenuated, vaccine within 2 months prior to the Baseline (Day 1) visit (participants must agree to avoid live vaccination, including live attenuated, during study treatment and within 3 months thereafter).
19) Any known hypersensitivity to any component of study treatment or other biologics (e.g., mAbs, fusion proteins).
20) 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.
21) Planned major surgical procedure during the study.
22) Participation in another research study involving an investigational product within 3 months prior to the Baseline (Day 1) visit.
23) 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: Solution for IV injection

Route of Administration: IV infusion

Dosage:

- Cohort 1: three infusions of IMG-007 [redacted] Q2W within 4 weeks.
- Cohort 2: three infusions of IMG-007 [redacted] Q2W within 4 weeks.

IMG-007 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 tests, if applicable
- Concomitant medications and procedures

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

- In-clinic assessments by investigators including:
  - Investigator's assessment of SALT score
  - Investigator's assessment of a target scalp lesion (IATS)
  - Investigator's global assessment of eyebrows (IGA-EB)
  - Investigator's global assessment of eyelashes (IGA-EL)
  - Investigator's global assessment of fingernails (IGA-FN)
- In-clinic assessments by participants including:
  - Patient's global impression of severity (PGIS) of AA (PGIS-AA) and AA on scalp (PGIS-S), eyebrows (PGIS-EB), eyelashes (PGIS-EL), and fingernails (PGIS-FN)
  - Patient's global impression of change (PGIC) in AA (PGIC-AA) and AA on scalp (PGIC-S), eyebrows (PGIC-EB), eyelashes (PGIC-EL) and fingernails (PGIC-FN)

    Note: Patients will be instructed to compare with their conditions before they started study treatment.
  - Alopecia areata patient priority outcomes (AAPPO)
  - Hospital anxiety and depression scale (HADS)

- Other assessment:
  - Photographs of the scalp at the four planes/views (left, right, top and back side) and the target scalp lesion

PK Assessments: Serum concentration of IMG-007 over time and by dose regimen 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: Blood samples will be collected for analysis of inflammatory markers and receptor occupancy. Scalp biopsy samples will be collected for histology, transcriptome analysis and immunohistochemical staining for tissue biomarkers.

Study Endpoints:

Primary Endpoint: Incidence of TEAEs

Secondary Endpoints

- Percentage change in SALT from baseline to Week 24

Statistical Plan:

Sample Size Determination

[redacted]

Analysis Sets

- Safety analysis set will be used for safety analyses, which will include all participants who received at least one dose of study treatment. Participants will be analyzed by the dose 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 who received at least one dose of study treatment.
- PK analysis set will be used for PK and ADA analyses, which will include all participants 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 in the safety analysis set who also have baseline and at least one post-baseline evaluable PD/biomarker data point.

Statistical Methods

Safety Analyses

Safety variables including incidence, severity, 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, the version currently in use by the Sponsor at the time of database lock). TEAEs are defined as events started after the 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 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 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, and standard deviation. Categorical efficacy variables will be summarized by

frequency and percentage for each category. Analysis will be presented by cohort (dose group) as well as the overall population (two cohorts pooled) if efficacy results across various endpoints by dose group are similar. In general, efficacy analyses will be descriptive based on observed data. For the key efficacy endpoints based on SALT score, besides the descriptive analyses, additional analyses will be planned, including mixed model repeated measure (MMRM) analysis and one sample t-test for percent (%) changes and absolute changes from baseline in SALT over time (by visit) up to Week 24 by dose group and in the pooled population (if efficacy results across various efficacy endpoints by dose group are similar), to evaluate if these changes are nominally significant. Various imputation methods will also be explored in addition to the observed value method. Treatment policy-based estimand will be used for all efficacy analysis. Further details including handling of specific intercurrent events and other imputation methods 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. The effect of immunogenicity on PK, efficacy and safety may be evaluated if data allows.

PD Analyses

Biomarker data will be listed by participant and visit/timepoint.

Timing of analyses

[redacted]

1.2 Schedule of Assessments

Table 1 Schedule of Assessments

Procedures	Screening	Treatment Period								Follow-up Period		Extended Follow-up Period post EOS	
		Baseline							EOT[21]	EOS[21]			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
		Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 30	Week 36
	Day -35 to -1	Day 1	Day 8	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169	Day 211	Day 253
Time window			± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 7d	± 7d
Informed consent[1]	X												
Demographics and medical history[2]	X												
Vital signs[3]	X	X	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	X	X
12-lead ECG	X	X							X		X		X
Inclusion/exclusion criteria	X	X											
Prior and concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and serum chemistry[5]	X	X	X	X	X	X	X	X	X	X	X		X
Total IgE[5]		X											
Urinalysis[5]	X	X		X	X				X		X		X
TB testing and TB risk follow up[5,6]	X								X		X		X
Viral disease screening[5,7]	X												
Pregnancy tests (WCBP only)[5,8]	X^{S}	X^{S+U}		X^{S+U}	X^{S+U}		X^{S}	X^{S}	X^{S}	X^{S}	X^{S}		X^{S}
Administration of study treatment[9]		X		X	X								
SALT, IGA-EB, IGA-EL, IGA-FN[10]	X	X			X	X	X	X	X	X	X	X	X
IATS[10]		X			X	X	X	X	X	X	X	X	X
PGIS-AA, PGIS-S, PGIS-EB, PGIS-EL, PGIS-FN[11], AAPPO[12], HADS[13]		X			X	X	X	X	X	X	X	X	X
PGIC-AA, PGIC-S, PGIC-EB, PGIC-EL, PGIC-FN[14]					X	X	X	X	X	X	X	X	X
PK sampling[15]		X	X	X	X	X	X	X	X	X	X		
ADA sampling[16]		X		X	X	X	X	X	X	X	X		

[redacted]

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 AA treatment, and surgical history. At the Baseline (Day 1) 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 blood pressure, pulse, respiratory rate 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. Physical examination: A full physical examination will be performed at Screening. A brief physical examination will be completed at the Baseline visit, and symptom-directed physical examinations will be completed at each follow-up (including the extended 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. The sample should be taken before dosing on dosing days.
6. All participants will undergo TB test (QuantiFERON-TB Gold [QFT-G] test or an equivalent test) at Screening. Participants who receive study treatment will be followed up by a TB risk assessment questionnaire (see Appendix 1: Tuberculosis Risk Assessment) at Week 16 (Day 113)/EOT, Week 24 (Day 169)/EOS and Week 36 (Day 253). 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.
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) visits, and at the selected follow-up (including the extended follow-up) visits. In addition, a urine pregnancy test must be performed prior to dosing at the Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) visits, which will be conducted at the study site.
9. On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes with a slower rate during the first 15 minutes. Participants will be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AEs observed have resolved or stabilized, whichever is longer. For diagnostic purposes, any participant who experiences any systemic infusion-related event should have a blood sample taken, ideally 30–60 minutes after the onset, for tryptase testing, and samples should be analyzed by a local laboratory if feasible. 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. If a dose is not administered on schedule due to a visit occurring beyond the visit window specified or due to dose interruption for reasons stated in Section 6.10.1.2, the dose may be administered if it is no later than 5 days after the allocated visit day (a 10-day delay will be allowed for the last dose at Week 4) specified. Otherwise, the dose will be considered missed, and dosing will resume with the next scheduled dose. The study site will contact the participants by telephone approximately 24 hours after the infusion for general AE query.
10. SALT, IATS, IGA-EB, IGA-EL, IGA-FN should be performed only by adequately trained investigators or sub-investigators. Efforts should be made that the same assessor performs the assessments of a particular participant throughout the study. IGA-EB, IGA-EL, IGA-FN will only be performed in participants with AA on eyebrows, eyelashes and/or nails.
11. Participants will complete the questionnaire for PGIS-AA, PGIS-S, PGIS-EB, PGIS-EL and PGIS-FN. PGIS-EB, PGIS-EL and PGIS-FN will only be performed in participants with AA on eyebrows, eyelashes and/or nails.
12. Participants will complete the AAPPO questionnaire to measure hair loss, emotional symptoms, and activity limitations over the past week.
13. Participants will complete the HADS to assess states of anxiety and depression over the past week.
14. Participants will complete the questionnaires for PGIC-AA, PGIC-S, PGIC-EB, PGIC-EL and PGIC-FN. PGIC-EB, PGIC-EL and PGIC-FN will only be performed in participants with AA on eyebrows, eyelashes and/or nails.
15. On dosing days, blood sample should be taken within 60 minutes before dosing and within 10 minutes after end of infusion.
16. On dosing days, blood sample should be taken within 60 minutes before dosing.

[redacted]

[redacted]

21. Participants who discontinue 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 16 visit should complete the Week 16 (Day 113)/EOT visit at withdrawal. Participants who withdraw from study early during the follow-up period should complete the Week 24 (Day 169)/EOS visit at withdrawal. Participants who discontinue early after the Week 24/EOS visit but before the Week 36 visit should complete Week 36 (Day 253) visit at withdrawal.

Abbreviations: AA = alopecia areata; ADA = anti-drug antibody; AAPPO= alopecia areata patient priority outcomes; AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EOI = end of infusion; EOS = end of study; EOT = end of treatment; HADS= hospital anxiety and depression scale; 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; IATS = investigator's assessment of a target scalp lesion; IGA-EB = investigator's global assessment of eyebrows; IGA-EL = investigator's global assessment of eyelashes; IGA-FN = investigator's global assessment of fingernails; IgE = immunoglobulin E; IV = intravenous; PD = pharmacodynamic; PGIC-AA = patient's global impression of change of alopecia areata; PGIC-EB = patient's global impression of change of alopecia areata on eyebrows; PGIC-EL = patient's global impression of change of alopecia areata on eyelashes; PGIC-FN = patient's global impression of change of alopecia areata on fingernails; PGIC-S= patient's global impression of change of alopecia areata on scalp; PGIS-AA = patient's global impression of severity of alopecia areata; PGIS- EB = patient's global impression of severity of alopecia areata on eyebrows; PGIS- EL = patient's global impression of severity of alopecia areata on eyelashes; PGIS-FN = patient's global impression of severity of alopecia areata on fingernails; PGIS-S = patient's global impression of severity of alopecia areata on scalp; PK = pharmacokinetic; S = serum; SALT= severity of alopecia tool; TB = tuberculosis; U = urine; V = visit; WCBP = women of childbearing potential

2 INTRODUCTION

2.1 IMG-007

IMG-007 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

As of the cut-off date of 10 February 2023, interim aggregate blinded data from 44 adult healthy participants who received a single dose of either IMG-007 up to [redacted] or placebo in the ongoing single ascending dose study (IMG-007-101) is available for assessing the clinical experience of IMG-007.

A total of 34 (77.3%) participants reported at least one treatment emergent adverse events (TEAEs). The most common TEAEs by preferred term were dermatitis contact (9 out of 44 participants [20.5%]), headache (6 out of 44 participants [13.6%]), and coronavirus disease 2019 (COVID-19; 5 out of 44 participants [11.4%]). There were no apparent differences in the incidence of TEAEs between the treatment cohorts and no dose-dependent trend for any TEAE.

All TEAEs were of mild (28 of 34) or moderate (6 of 34) intensity. All TEAEs were judged to be unrelated to the study treatment with the exception that one participant who received either IMG-007 3 mg or placebo experienced a TEAE of mild catheter site-related reaction. All TEAEs were recovered/resolved by the data cut-off date. No localized or systemic infusion-related reactions were reported in the study to date. Further details can be found in the Investigator's Brochure (IB).

2.3 Alopecia Areata

Alopecia areata (AA) is a chronic relapsing and remitting autoimmune disease characterized by nonscarring hair loss involving the scalp, face, and/or body. It can affect children and adults of all ages, races and genders but more commonly in females and non-whites especially Asians (Mostaghimi et al 2023; Harries et al 2022). Approximately 2% of the general population can be affected by AA during their lifetime (Pratt et al 2017). The point prevalence rates of AA based on recent studies using electronic healthcare records were approximately 0.22% in the United States (US) (Mostaghimi et al 2023) and 0.58% in the United Kingdom (Harries et al 2022).

AA typically presents with well-demarcated patches of hair loss, most commonly on the scalp, but it may also involve the beard, eyebrows, eyelashes, and nails. In severe cases, AA involves the full scalp (alopecia totalis [AT]) or even full body (alopecia universalis [AU]). AA involving 50% or greater scalp hair loss, including AT and AU, is considered an advanced form (King, Senna et al 2022; King, Mesinkovska et al 2022). AA is associated with other inflammatory and autoimmune diseases including atopic diseases (e.g., atopic dermatitis [AD] and allergic rhinitis), autoimmune diseases (e.g., thyroiditis, lupus erythematosus), metabolic syndrome, and psychiatric disorders (Lee et al 2019). AA significantly impacts patients' daily life and often leads to profound psychological distress, social isolation, anxiety, and depression (Pratt et al 2017; Mesinkovska et al 2020).

The exact pathogenesis of AA is not fully understood. It involves a complex interplay between genetics, environmental factors, and adaptive immune response to unknown antigens. It is thought that the collapse of follicular immune privilege leads to activation and infiltration of immune cells, primarily $CD4^+$ and $CD8^+$ T cells, and also natural killer cells, mast cells, and dendritic cells, which swam and attack the hair bulbs (Bertolini et al 2020; Olayinka et al 2021). Hair follicle cells in turn release more cytokines and chemokines that further recruit T cells and other immune cells forming positive feedback loops that shorten and distort the hair cycle. Activation of T cell subsets including T-helper (Th) type 1 (Th1) and Th2 cells in AA patients is associated with disease severity or chronicity (Czarnowicki et al 2018; Glickman, Dubin, Renert-Yuval et al 2021).

Current treatment options for AA are limited. They include topical, intralesional, and systemic agents. Topical treatments (e.g., topical corticosteroids, calcineurin inhibitors, diphenylcyclopropenone [DPCP], squaric acid, and minoxidil) have limited efficacy and are not suitable for large areas or long-term use. Intralesional corticosteroids are also not applicable for large areas and chronic use. Oral corticosteroids and conventional immunosuppressants (e.g., cyclosporine A, mycophenolate mofetil [MMF], and azathioprine) are used off-label, with limited evidence from randomized controlled trials regarding their benefit/risk profiles in AA patients. These immunosuppressive agents are often associated with adverse events (AEs) that prevent their long-term use. (Meah et al 2020). Although oral Janus kinase (JAK) inhibitor baricitinib was recently approved by the US Food and Drug Administration (FDA) for severe and very severe AA, potential serious safety risks would limit its use for chronic management of AA (OLUMIANT 2022). There remain significant unmet needs for safe and effective novel targeted systemic therapies for long-term treatment of AA.

2.4 Rationale for IMG-007 in Alopecia Areata

Emerging evidence supports an important role of OX40–OX40L signaling in promoting the proliferation and survival of T cells and augmenting the clonal expansion and function of effector and memory T cells, thereby mediating the pathogenesis of a spectrum of inflammatory and autoimmune diseases including AD and AA (Webb et al 2016; Guttman-Yassky et al 2023; Iriki et al 2023).

A genetic mapping study in AA patients revealed that an OX40L genetic locus is associated with susceptibility to AA (Redler et al 2015). OX40L/OX40 interaction is required for the activation of $CD4^+$ and $CD8^+$ T cell as well as recruitment of other immune cells (Nakae et al 2005; Bulfone-Paus et al 2015). In AA, activated T cells interact with other immune cells such as mast cells in amplifying follicular inflammation. Aggregation of peri- and intrafollicular $OX40^+$ T cells and their physical contacts with $OX40L^+$ mast cells were observed in AA hair follicles (Bertolini et al 2014). Separately, elevated OX40 gene expression has been shown in AA lesional scalp (Glickman, Dubin, Dahabreh et al 2021).

AA and AD coexist in many patients. Based on a systemic review and meta-analysis, 9.6% of AA patients have comorbid AD (Lee S et al. 2019). The two diseases share overlapping molecular profiles including important roles of OX40–OX40L interactions in the disease pathogenesis (Elsner et al 2020; Iriki et al 2023). mAbs targeting OX40 rocatinlimab (KHK4083) and telazorlimab (GBR 830) have shown remarkable clinical effect in improving skin signs in AD patients (Guttman-Yassky et al 2023; Nakagawa et al 2020; Guttman-Yassky et al 2019). The clinical evidence of OX40 antagonists in AD supports a similar role of OX40–OX40L signaling in AA.

The above evidence suggests that OX40 is a promising target for AA. IMG-007 is a humanized IgG1 subclass mAb that specifically targets human OX40 with high affinity and inhibits OX40L-induced signaling. Modifications in the Fc region were made to remove glycosylation and abolish antibody-dependent cellular cytotoxicity (ADCC). IMG-007 represents a promising therapeutic candidate for the treatment of AA.

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, pharmacokinetics (PK) and pharmacodynamics (PD) of IMG-007 in the target patient population, i.e., adult participants with advanced AA (defined as severity of alopecia tool [SALT] score ≥ 50). The study population represents a subset of AA patients who are candidates for systemic therapy, for which there remains a significant unmet need.

Since spontaneous remission is rare in AA patients with advanced disease (e.g., with at least 50% scalp hair loss), and the placebo effect observed in this population in other trials was fairly low (King et al 2021; King, Ohyama, Kwon et al 2022), the open-label design proposed in this study is considered adequate for initial characterization of efficacy of IMG-007 in improving hair loss in the study population.

The study includes a 16-week treatment period and an 20-week follow-up period. The proposed 16-week treatment period is based on a 4-week dosing duration, which is estimated to result in a reasonable level of IMG-007 systemic exposure by Week 16 (i.e., 12 weeks after the last dose of study treatment at Week 4) when a clinically meaningful improvement in scalp hair loss is anticipated (see Section 2.5.2). Based on the observation that treatment with mAbs against OX40 for as short as 4 weeks provided clinically meaningful and durable improvements in AD symptoms for up to 18 weeks after the last dose of study treatment (Guttman-Yassky et al 2019; Nakagawa et al 2020; Guttman-Yassky 2023). Recent phase 2b study of amlitelimab, an anti-OX40L antibody, showed a durable clinical response for up to 28 weeks after drug withdrawal, despite minimal remaining serum concentrations of study drug (Weidinger et al 2024). A similarly enduring clinical effect may be expected for OX40/OX40L antagonism in AA, even with low drug exposure. Moreover, clinical studies in AA have shown that onset to visible hair regrowth was generally slow especially for targeted biologics; hence most trials evaluate key efficacy endpoints at Week 24 and Week 36 (King et al 2021, Guttman-Yassky et al 2022). Based on the above considerations, the timing of the secondary efficacy assessment has been revised from Week 16 to week 24, and an extended follow-up period post EOS was added to assess potential further clinical improvement beyond Week 24 up to Week 36. Separately, the follow-up period can 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 AA participants. The key variables include SALT score, other investigator's assessments, and patient reported outcomes. The clinical and laboratory assessments for safety and tolerability 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]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.6 Summary of Benefits and Risks

Clinical effects of IMG-007 in AA patients have not been assessed. Based on the AA pathogenesis and mechanism of action of IMG-007, it is hypothesized that IMG-007 would exhibit clinical activities in AA patients.

Considering that IMG-007 is an investigational therapeutic protein and its mechanism of targeting OX40-OX40L signaling, as well as the 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 [redacted], no localized or systemic 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 [redacted] to the [redacted] dose level. The decision of escalation to [redacted] will be made only after all six participants in the 300 mg group have completed the Week 2 (Day 15) visit (i.e., after two doses) with verification of safety per the dose escalation criteria (Section 4.1.1). During this study, participants will receive IV infusions over approximately 60 minutes with a slower rate during the first 15 minutes and will be closely monitored during and after drug administration.

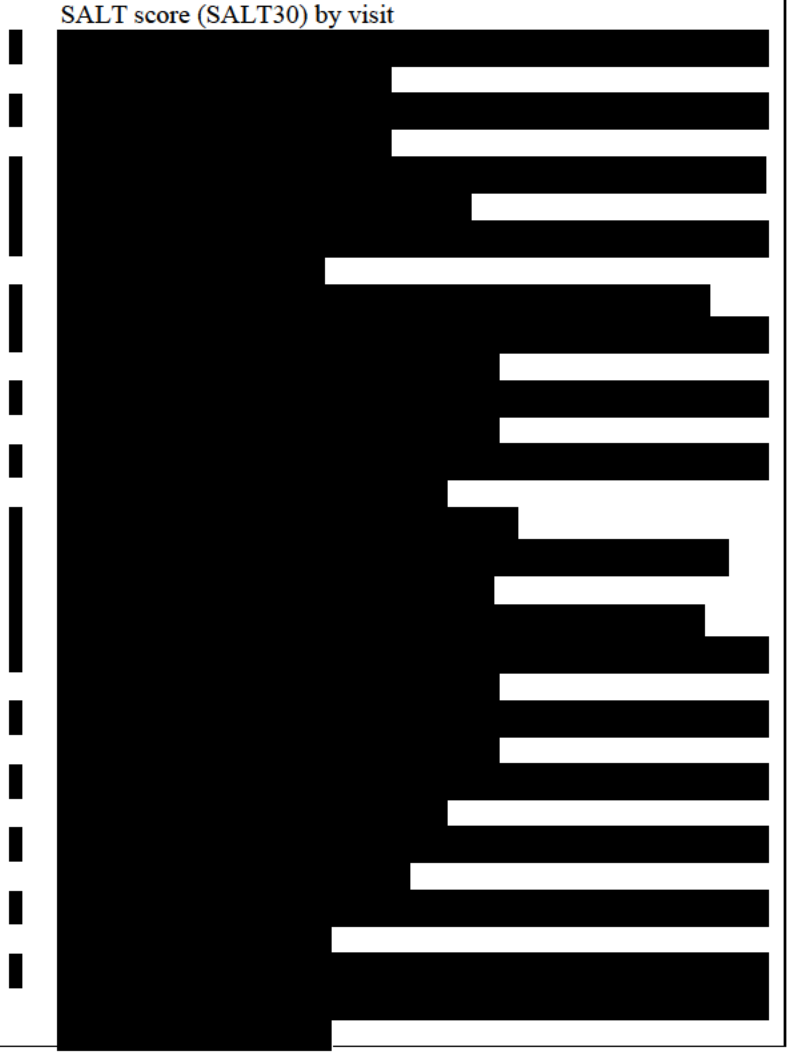
The inclusion and exclusion criteria are intended for enrollment of AA participants who are candidates for systemic therapies and for whom potential safety risks from participating in the study are considered acceptable. The overall risk to participants is minimized by excluding participants with comorbidities 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 AA	Incidence of TEAEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of multiple doses of IMG-007 in AA participants as measured by SALT at Week 24	Percentage change in SALT from baseline to Week 24
Exploratory Objectives	**Exploratory Endpoints**
To further evaluate the efficacy of multiple doses of IMG-007 in AA participants as measured by SALT and other investigator's assessments and patient reported outcomes	• Absolute and percentage changes from baseline in SALT by visit • Proportion (%) of participants achieving a 30% improvement in SALT score (SALT30) by visit 

Abbreviations: AA = alopecia areata; AAPPO = Alopecia areata patient priority outcomes; ADA= anti-drug antibody; AE = adverse event; CL= central compartment clearance; EB = eyebrows; ECG = electrocardiogram; EL = eyelashes; FN = fingernails; HADS = Hospital anxiety and depression scale; IATS = Investigator's assessment of a target scalp lesion; IGA = Investigator's global assessment; PD = pharmacodynamic; PGIC = patient global impression of change; PGIS = patient global impression of severity; PK = pharmacokinetic; S = scalp; SALT = Severity of Alopecia Tool; TEAE = treatment-emergent adverse event; Vc= central compartment volume

4 STUDY DESIGN

4.1 Overall Study Design

This is a phase 1b/2a, open label, dose escalation study to assess the safety, PK, efficacy, and PD of multiple doses of IMG-007 in participants with AA. Approximately 30 participants will be enrolled. The study will consist of two dose cohorts to be initiated sequentially in ascending dose order: Cohort 1 with six participants receiving three IV infusions of IMG-007 over 4 weeks and Cohort 2 with 24 participants receiving three IV infusions of IMG-007 over 4 weeks (Figure 2).

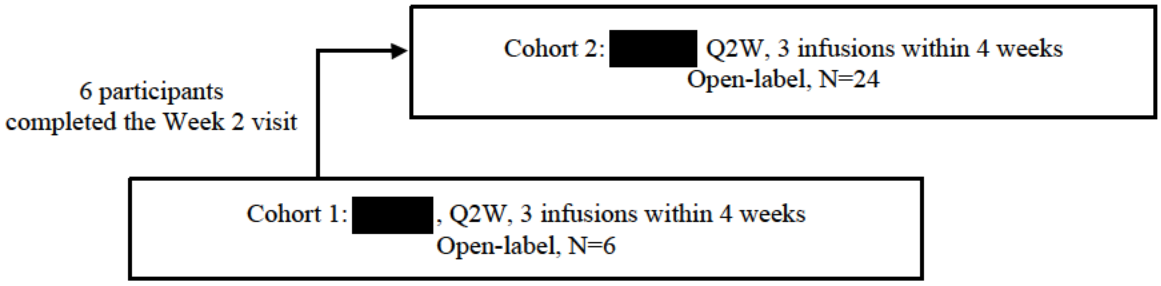


Figure 2 Study Schema

4.1.1 Dose Escalation Criteria

[redacted]

4.1.2 Study Period

Each dose cohort will consist of four periods: a screening period of up to 5 weeks, a 16-week treatment period, an 8-week follow-up period, and a 12-week extended follow-up period post EOS.

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.

Treatment Period: Day 1 (Baseline) to Day 113 (16 weeks)

Participants who meet all eligibility criteria will be enrolled and will receive three IV infusions of IMG-007 [redacted] or [redacted] administered 2 weeks apart at the Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) visits. The study site will contact participants by telephone approximately 24 hours after each infusion for assessment of AEs and/or concomitant medications.

On dosing days, study treatment will be administered as an IV infusion over approximately 60 minutes with a slower rate during the first 15 minutes. Participants will be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AEs observed 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 should be analyzed by a local laboratory if feasible. Study sites should have access to equipment or facilities for the management of potential hypersensitivity reactions.

Beyond dosing visits, participants will complete visits at Week 1 (Day 8), Week 6 (Day 43), Week 8 (Day 57), Week 12 (Day 85) and Week 16 (Day 113)/end of treatment (EOT).

Follow-up Period: Day 113 to Day 169 (8 weeks)

The follow-up period consists of two visits: Week 20 (Day 141) and end of study (EOS; Week 24 [Day 169]) Visits.

Extended Follow-up Period Post EOS: Day 169 to 253 (12 weeks)

The extended follow-up period after EOS consists of two visits: Week 30 (Day 211) and Week 36 (Day 253).

The schedule of assessments (SoA) at each visit is summarized in Table 1. Assessments of efficacy, safety will be conducted throughout this study (until extended follow-up period post EOS) and PK, PD, and immunogenicity data will be collected until the end of EOS visit.

Participants who discontinue 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 16 visit should complete the Week 16 (Day 113)/EOT visit at withdrawal.

Participants who withdraw from study early during the follow-up period should complete the Week 24 (Day 169)/EOS visit at withdrawal.

Participants who discontinue early after the Week 24/EOS visit but before the Week 36 visit should complete Week 36 (Day 253) visit at withdrawal.

A participant who withdraws from the study prior to receiving two doses of study treatment (i.e., completing the Week 2 visit) for reasons other than AEs will be replaced.

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 (including the extended 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 AA. Eligibility criteria include the following.

5.1 Inclusion Criteria

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

1) Male or female aged ≥ 18 and ≤ 65 years when signing the consent form.

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) Clinical diagnosis of AA with current episode of hair loss of [redacted] prior to the Screening visit.

4) No evidence of terminal hair regrowth within [redacted] prior to the Screening and Baseline (Day 1) visits.

5) AA with ≥ 50% scalp involvement as defined as SALT score ≥ 50 (of total 100), including AT and AU, at the Screening and Baseline (Day 1) visits.

   Note: Recruitment of participants with AT or AU will be limited to no more than 10% (i.e., up to one participant in Cohort 1 and up to two participants in Cohort 2).

6) 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.

7) Male participants must agree to practice true abstinence; 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 with female partners of childbearing potential and must also agree not to donate sperm.

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:
   - HBV: Positive test for hepatitis B surface antigen (HBs Ag), OR positive test for hepatitis B core antibody (HBcAb) with negative test for hepatitis B surface antibody (HBsAb)
   - HCV: Positive test for hepatitis C antibody
   - HIV: Positive test for HIV antibody

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

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 Baseline (Day 1) visit.

7) Concurrent hair loss due to other etiologies including but not limited to androgenetic alopecia (only exclude Ludwig Type ≥ II for female pattern or Norwood-Hamilton Stage ≥ IV for male pattern), traction and scarring alopecia, trichotillomania, telogen effluvium, and drug-induced hair loss.

8) Primarily "diffuse" type of AA.

9) Active inflammatory diseases on the scalp (e.g., tinea capitis, scalp psoriasis, seborrheic dermatitis) that would interfere with the assessment of AA based on the investigator's clinical judgement.

10) History or presence of hair transplants or micropigmentation of the scalp.

Note: microblading of the eyebrows is permitted.

11) Active systemic diseases that may cause hair loss (e.g., thyroiditis, systemic lupus erythematosus, iron deficiency).

12) Use of topical treatments for AA within 2 weeks before the Baseline (Day 1) visit, such as corticosteroids, calcineurin inhibitors, JAK inhibitors (e.g., ruxolitinib), antimicrobials, anthralin, DPCP, squaric acid, minoxidil or any other medication which, in the opinion of the investigator, may affect hair regrowth.

Note: Topical treatments are permitted outside of the scalp, eyebrows and eyelashes.

13) Use of non-biologic systemic (oral or injectable) agents, including conventional immunosuppressants or immunomodulators (e.g., corticosteroids, dapsone, methotrexate, MMF, cyclosporine A, azathioprine, hydroxychloroquine, sulfasalazine, and other approved drugs) within 4 weeks or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit.

14) Use of oral JAK inhibitors within 8 weeks prior to the Baseline (Day 1) visit.

Note: Recruitment of participants with a history of inadequate response (defined as failure to achieve ≥ 50% improvement in hair loss [equivalent to ≥ 50% improvement in SALT score] after approximately 6 months of treatment) to a JAK inhibitor will be limited to no more than 20% (i.e., up to one participant in Cohort 1 and up to five participants in Cohort 2).

15) Use of oral or injectable agents (minoxidil, apremilast, finasteride, hydroxymethylglutaryl coenzyme A [HMG-CoA] reductase inhibitors [statins], herbal medicines) for the treatment of AA within 4 weeks prior to the Baseline (Day 1) visit.

16) Use of biologic therapy (e.g., mAbs against interleukin [IL]-17, IL-4, and IL-13 or other investigational products) or platelet-rich plasma within 3 months or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit.

17) Use of phototherapy for the treatment of AA with ultraviolet (UV) A or UVB or any other type of light therapy that, in the opinion of the investigator, may affect hair regrowth within 4 weeks before the Baseline (Day 1) visit.

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

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

20) 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.

21) Planned major surgical procedure during the study.

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

23) 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/randomized 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 be assigned a new subject number (including signature of ICF) 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

The study is open label and consented participants meeting all eligibility criteria will be enrolled into the study and assigned a unique enrollment number. Enrollment numbers are allocated sequentially in the order in which the participants are enrolled. Approximately 30 participants will be enrolled.

6.2 Treatment Blinding

This will be an open-label study.

6.3 Investigational Product Supply

IMG-007 will be supplied by the Sponsor and labeled appropriately as an 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 an 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 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 will be in accordance with Good Manufacturing Practice and Good Clinical Practice (GCP) and any other local regulatory requirements.

Each vial of IMG-007 will have a one-piece label attached to it and will be placed in a carton. The carton will have a one-piece label attached with the following information included: the 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. 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.

6.4 Dosing and Administration

IMG-007 should be administered via IV infusion.

Participants will receive IMG-007 [redacted] (Cohort 1) or [redacted] (Cohort 2) 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 with a slower rate during the first 15 minutes. Participants will be closely monitored at the study site for a minimum of 1 hour after completion of each infusion or until any AE 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.

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 days after the allocated visit day (a 10-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 are 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 AE 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 should be analyzed by a local laboratory if feasible.

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 criteria defined in Sampson et al 2006 and summarized in Appendix 2) 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 treatment before the Week 4 visit should continue with all the remaining study visits.

6.7 Investigational Product Storage, Accountability and Disposal

IMG-007 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 an investigator, pharmacist, study nurse, or any medically qualified personnel with documented appropriate qualifications and training and authorized by the investigator according to local regulations, following 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.

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) will be accounted for in accordance with GCP. There will be an investigational product accountability record with information for each subject 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 clinical drug supplies were received, dispensed, administered, disposed and returned to the Sponsor. If temperature excursion or damage occur to the clinical drug 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 subjects of this trial, according to the procedures described in this trial 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 responsibility 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 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 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 stable regimen 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:

- Use of topical treatments for AA within 2 weeks before the Baseline (Day 1) visit and until completion of the follow-up (including the extended follow-up) period, such as corticosteroids, calcineurin inhibitors, JAK inhibitors (e.g., ruxolitinib), antimicrobials, anthralin, DPCP, squaric acid, minoxidil or any other medication which, in the opinion of the investigator, may affect hair regrowth;

  Note: Topical treatments are permitted outside of the scalp, eyebrows and eyelashes.

- Use of non-biologic systemic (oral or injectable) agents including conventional immunosuppressants or immunomodulators (e.g., corticosteroids, methotrexate, MMF, cyclosporine A, azathioprine, hydroxychloroquine, sulfasalazine 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 (including the extended follow-up) period;

- Use of oral JAK inhibitors within 8 weeks prior to the Baseline (Day 1) visit and until completion of the follow-up (including the extended follow-up) period;

- Use of oral or injectable agents (minoxidil, apremilast, finasteride, HMG-CoA reductase inhibitors [statins], herbal medicines) for the treatment of AA within 4 weeks prior to the Baseline (Day 1) visit and until completion of the follow-up (including the extended follow-up) period;

  *Note that the listed medications are permitted if they are not indicated for the treatment of AA **AND** have been used at a stable dose until the completion of the study. These medications are prohibited if they are indicated for the treatment of AA **OR** if they have been newly initiated or had their dose modified during the study.*

- Use of any biologic therapy (e.g., mAbs against IL-17, IL-4, and IL-13 or other investigational products) or platelet-rich plasma within 3 months or 5 half-lives, whichever is longer, prior to the Baseline (Day 1) visit and until completion of the follow-up (including the extended follow-up) period;

- Use of phototherapy for the treatment of AA within 4 weeks before the Baseline (Day 1) visit and until completion of the follow-up (including the extended follow-up) period, such as UVA or UVB, or any other type of light therapy that, in the opinion of the investigator, may affect hair regrowth.

- Receipt of a live vaccine, including live attenuated, within 2 months before the Baseline (Day 1) visit and until 3 months after the last administration.

- Other medications or non-drug therapies, in the opinion of the investigator, that could affect AA from screening to study completion.

6.10 Early Withdrawal from Study

6.10.1 Discontinuation of Study Treatment

6.10.1.1 Permanent Discontinuation of Study Treatment

[redacted]

[redacted]

- 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. If study treatment is discontinued early, efforts should be made to perform the remaining study visits through EOS.

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 the 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 the 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

If a participant cannot or will not continue in the trial, the participant should complete the EOS visit procedures instead of the planned visit. All information, including the reason for early withdrawal, will be recorded in the participant's study records and in the case report form (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 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/independent ethics committee (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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the 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

[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 who 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.

Safety laboratory analysis will be performed centrally. 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 must be confirmed at the Baseline (Day 1) visit before any other assessment/procedure is performed.

Participants will receive three IV infusions of IMG-007 [redacted] or [redacted] administered 2 weeks apart at the Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) visits. Participants will complete additional visits at Week 1 (Day 8), Week 6 (Day 43), Week 8 (Day 57), Week 12 (Day 85) and Week 16 (Day 113)/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 at the Baseline (Day 1), Week 2 (Day 15), and Week 4 (Day 29) visits.

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.

The investigator may discontinue a participant's study treatment at any time during the study when the participant meets the study treatment discontinuation criteria described in Section 6.10.1.

In addition, every effort should be made to perform all procedures scheduled for the EOT visit. Study staff will record the AE(s) as reported by the participant or observed by the investigator. They will record vital signs, results of the 12-lead electrocardiogram (ECG), or other assessments, including the information to be recorded. Study staff will collect blood/urine for the appropriate laboratory tests. They will also record the participant's adherence to protocol procedures.

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, PD, 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 at Week 24 (Day 169).

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.

7.1.6 Extended Follow-up Period Post EOS

Participant will return to the study center for extended follow-up period visits post EOS and complete the procedures for safety and efficacy evaluations. The details for extended follow-up procedures are outlined in the SoA (Table 1).

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 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 study source document.

b) If any abnormalities are found in urinalysis, then microscopy should be conducted to examine the 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 the selected follow-up (including the extended follow-up) visits. In addition, urine pregnancy tests must be performed prior to dosing at the Baseline (Day 1), Week 2 (Day 15) and Week 4 (Day 29) visits.

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

Abbreviations: HBcAb = antibody to hepatitis B core antigen; HBsAb= hepatitis B surface antibody; HBsAg= hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgE = immunoglobulin E; TB = tuberculosis

7.2.3 Vital Signs and Physical Examination

Vital signs will be measured in semi-supine or supine position after 5 minutes of rest and will include temperature, respiratory rate, 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. Height and weight will also be measured and recorded. 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 (including the extended 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 the ECGs 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) and Week 4 (Day 29) visits, and at the selected follow-up (including the extended follow-up) visits. In addition, a 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 throughout the duration of the study.

Serum pregnancy tests will also be performed additionally whenever potential pregnancy is suspected. Additional pregnancy tests may also be undertaken if requested by the IRB/EC 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.

All assessments will be recorded in the eCRF according to the completion guidelines.

7.3.1 Severity of Alopecia Tool

SALT is a quantitative assessment of AA severity by the investigator based on scalp terminal hair loss. The investigator utilizes a visual aid showing the division of the scalp hair in four quadrants, with the top constituting 40%, the back 24%, and the right and left side of the scalp of 18% each of the total

surface (Olsen et al 2004). A composite score is derived based on the percentage of terminal hair loss in each of the four scalp views (areas). The SALT score will range from 0 to 100.

Further details on SALT scoring will be provided in the Study Reference Manual.

7.3.2 Investigator's Assessment of a Target Scalp Lesion

A target scalp lesion that best represents the overall severity (50% or greater hair loss) of AA, in the upper parietal region of scalp, if feasible, will be selected at the Baseline (Day 1) visit. The same target scalp lesion will be assessed at all subsequent visits.

At the scheduled clinic visits, the investigator will rate the severity of target scalp lesion as it looks on the day of study visit on a 5-point scale ranging from 0 = "no" to 4 = "very severe".

The investigator's assessment of a target scalp lesion (IATS) will be performed by the investigator. Further details on IATS will be provided in the Study Reference Manual.

7.3.3 Investigator's Global Assessment of Eyebrows

At the scheduled clinical visits, the investigator will rate the severity of eyebrow hair loss as it looks on the day of study visit on a 5-point scale ranging from 0 = "no" to 4 = "very severe".

The investigator's global assessment of eyebrows (IGA-EB) will be performed by the investigator. Further details on IGA-EB will be provided in the Study Reference Manual.

7.3.4 Investigator's Global Assessment of Eyelashes

At the scheduled clinical visits, the investigator will rate the severity of eyelash hair loss as it looks on the day of study visit on a 5-point scale ranging from 0 = "no" to 4 = "very severe".

The investigator's global assessment of eyelashes (IGA-EL) will be performed by the investigator. Further details on IGA-EL will be provided in the Study Reference Manual.

7.3.5 Investigator's Global Assessment of Fingernails

At the scheduled clinical visits, the investigator will rate the severity of fingernail changes as it looks on the day of study visit on a 5-point scale ranging from 0 = "no" to 4 = "very severe".

The investigator's global assessment of fingernails (IGA-FN) will be performed by the investigator. Further details on IGA-FN will be provided in the Study Reference Manual.

7.3.6 Patient's Global Impression of Severity of Alopecia Areata

At scheduled clinic visits, participants will be asked to rate patient's global impression of severity (PGIS) of their overall AA (PGIS-AA) and AA on the scalp (PGIS-S), eyebrows (PGIS-EB), eyelashes (PGIS-EL), and fingernails changes (PGIS-FN) using a 5-point scale ranging from 0 = "none" to 4 = "very severe".

Further details on PGIS-AA, PGIS-S, PGIS-EB, PGIS-EL and PGIS-FN will be provided in the Study Reference Manual.

7.3.7 Patient's Global Impression of Change of Alopecia Areata

At scheduled clinic visits, participants will be asked to rate patient's global impression of change (PGIC) in AA (PGIC-AA) and AA on scalp (PGIC-S), eyebrows (PGIC-EB), eyelashes (PGIC-EL), and fingernails (PGIC-FN) using 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 they started taking study treatment.

Further details on PGIC-AA, PGIC-S, PGIC-EB, PGIC-EL and PGIC-FN will be provided in the Study Reference Manual.

7.3.8 Alopecia Areata Patient Priority Outcomes

The alopecia areata patient priority outcome (AAPPO) scale is a participant self-administered 11-item questionnaire that measures hair loss (4 items using a 5-point scale), emotional symptoms (4 items using a 5-point scale), and activity limitations (3 items using a 5-point scale) over the past week (Wyrwich et al 2022).

The AAPPO is completed by the participant in the study clinic. Further details on AAPPO will be provided in the Study Reference Manual.

7.3.9 Hospital Anxiety and Depression Scale

The hospital anxiety and depression scale (HADS) is a 14-item self-assessment scale that determines the levels of anxiety (7 items) and depression (7 items) that a patient is experiencing over the past week. The HADS utilizes a 4-point Likert response scale (e.g., 0 to 3) for each item. Scores for each domain (anxiety and depression) can range from 0 to 21, with higher scores indicating greater anxiety or depression (Zigmond et al 1983).

The HADS is completed by the participant in the study clinic. Further details on HADS will be provided in the Study Reference Manual.

7.3.10 Photography of Alopecia Areata

In AA trials, photographs are important for assessing changes related to study treatment by comparing those taken at the Baseline (Day 1) and post-baseline visits. For all participants, photographs of the scalp at the four planes/views (left, right, top, and back side) and the target scalp lesion (a representative area of AA used for IATS assessments) will be taken at the Baseline (Day 1), Week 16 (Day 113)/EOT, Week 24 (Day 169)/EOS, Week 30 (Day 211), and Week 36 (Day 253) visits. Additional photographs, especially those recording specific changes noted are also encouraged, if the participant is willing.

For participants with AA on eyebrows, eyelashes and/or nails at the Baseline (Day 1) visit, photographs in these areas at the Baseline (Day 1), Week 16 (Day 113)/EOT, Week 24 (Day 169)/EOS, Week 30 (Day 211), and Week 36 (Day 253) visits are desirable but not mandated. Additional

photographs, especially those recording specific changes noted are also encouraged, if the participant is willing.

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 and documenting the photographs are provided in the Photography Manual.

7.4 Pharmacokinetic and Immunogenicity Assessments

Blood will be collected to describe the PK and immunogenicity profiles of IMG-007 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 anti-drug antibody (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 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-/Post-dose	PK sampling time	ADA sampling time	Sampling Window
1	1	Pre-dose	0	0	-60 mins
	1	Post-dose	EOI	--	+10 mins
	8	Post-dose	7 days post-dose	--	±3 days
2	15	Pre-dose	0	0	-60 mins
	15	Post-dose	EOI	--	+10 mins
3	29	Pre-dose	0	0	-60 mins
	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	Post-dose	56 days post-dose	56 days post-dose	±3 days
	113/EOT	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 Pharmacodynamic Assessments

Blood samples and scalp biopsy will be collected for biomarker analysis.

Details concerning the sampling instructions, handling of samples, labeling and shipping instructions are provided in the Laboratory Manual.

[redacted]

The biopsy should be taken from the edge of a lesion (not the center), and preferably from a lesion located at a site normally resistant to androgenetic alopecia.

Further details on collecting, processing, and shipping biopsy specimens will be provided in the Laboratory Manual.

Scalp biopsies will be analyzed for transcriptome sequencing, histology, and immunohistochemical staining for tissue biomarkers.

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 8.2.3.1).

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 purposes 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 the Baseline (Day 1) visit. 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 AE, severity should be assessed using the NCI 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?

8.2 Method of Detecting and Collecting Adverse Events

Care will be taken to not 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

All AEs/SAEs will be collected from the time the participant signs the ICF until the completion of the follow-up period (including the extended follow-up). After the follow-up period (including the extended follow-up), 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 values and 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., dose modification, 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 to urgent queries immediately but no later than 24 hours of when he or she receives the queries.

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

8.4 Pregnancy Report

All pregnancy events must be reported in the period starting from the first dose through completion of the follow-up (including the extended follow-up) period. 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 convene to review safety data, dose escalation criteria, and the study stopping criteria. The CRO and Sponsor medical monitors 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 US FDA, 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

[redacted]

[redacted]

11.2 Analysis Sets

- Safety analysis set will be used for safety analyses, which will include all participants who received at least one dose of study treatment. Participants will be analyzed by the dose 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 who received at least one dose of study treatment.

- PK analysis set will be used for PK and ADA analyses, which will include all participants 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 in the safety analysis set who also have baseline and at least one post-baseline evaluable PD/biomarker data point.

11.3 Statistical Analysis

11.3.1 Analysis of Safety

Safety variables including incidence, severity, 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, the version currently in use by the Sponsor at the time of database lock). TEAEs are defined as events started after the 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 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, including changes from baseline, where appropriate, will be summarized using descriptive statistics, by post-dosing shift from baseline 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

Efficacy analyses will be descriptive. Continuous efficacy variables will be summarized using descriptive statistics which will include mean, median, minimum, maximum, Q1 and Q3, and standard deviation. Categorical efficacy variables will be summarized by frequency and percentage for each category. Analysis will be presented by cohort (dose group) as well as the overall population (two cohorts pooled) if efficacy results across various endpoints by dose group are similar. Where appropriate, 95% confidence intervals will be provided. Subgroup analysis will also be conducted, as appropriate. No inferential analysis is planned. Analysis will also be presented for the overall population as well as by dose group.

In general, efficacy analyses will be descriptive based on observed data. For the key efficacy endpoints based on SALT score, besides the descriptive analyses, additional analyses will be planned, including mixed model repeated measure (MMRM) analysis and one sample t-test for percent (%) changes and absolute changes from baseline in SALT over time (by visit) up to Week 24 by dose group and in the pooled population (if efficacy results across various efficacy endpoints by dose group are similar), to evaluate if these changes are nominally significant. [redacted]

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. The effect of immunogenicity on PK, efficacy and safety may be evaluated if data allows.

11.3.5 Analysis of Pharmacodynamics Endpoints

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

Scalp biopsy data will be listed and summarized by visit.

11.3.6 Analysis of Exploratory and Other Endpoints

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

11.3.7 Interim Analysis

A first interim analysis (IA) may be performed when all participants have completed the Week 24 (Day 169) visit or discontinued early prior to Week 24 visit. A second IA may be performed when all participants have completed the Week 30 (Day 211) visit or discontinued early prior to Week 30 visit.

Final analysis will be performed when all participants have completed the study (i.e., Week 24 [Day 169]/EOS visit or the Week 36 [Day 253] visit, as applicable) or discontinued early. Details of the IA and the final analysis will be provided in the SAP.

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), 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 by 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 by 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 patient's name, full date of birth, or any other information which can identify the patient. All personal information shall be replaced with a Subject Identification Code (SID) code before any information leaves the investigative 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 the 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 and 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 12 in accordance with 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 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is a reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for 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 of subjects by the investigator (evaluated after a reasonable amount of time)
- Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/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.

12.8 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.

12.9 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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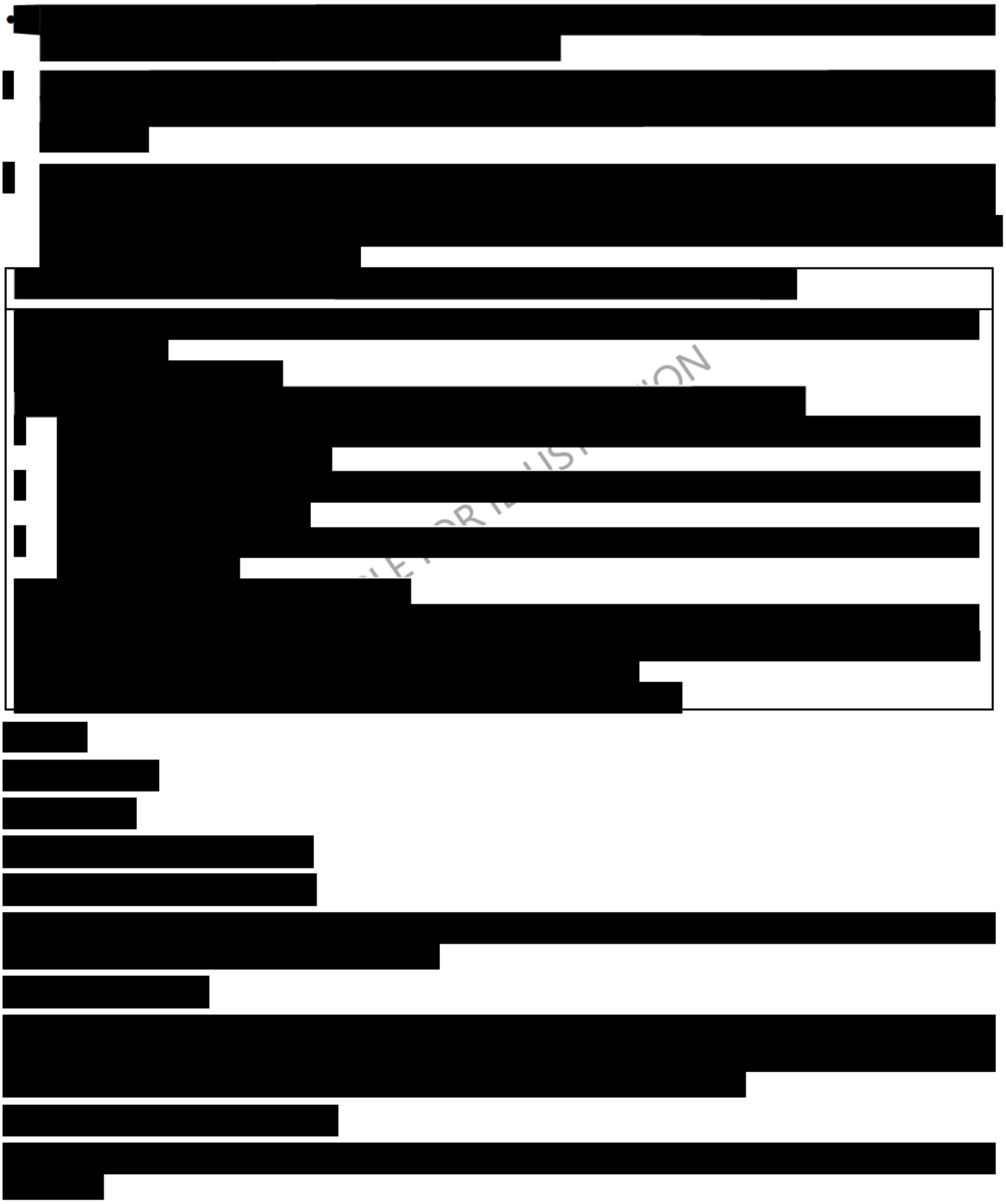
14 APPENDICES

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.

14.3 Appendix 3: Prior Protocol Amendments

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]

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

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

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]