Revised Clinical Study Protocol: VIS954-101

Protocol Title:	A phase 1, randomized, placebo-controlled, double-blind, single ascending dose, first-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of VIS954 in healthy male and female participants
Protocol Number:	VIS954-101
Compound:	VIS954
Brief Title:	A study to investigate the safety, pharmacokinetics, and pharmacodynamics of VIS954 in healthy adult participants
Study Phase:	Phase 1
Sponsor:	Visterra Inc., an Otsuka subsidiary
Address:	275 2nd Avenue, Waltham, MA 02451, United States
Immediately Reportable Event:	IQVIA E-mail: CCI [redacted]
IND Number:	160,895
Amendment 1 Approval Date:	20 Oct 2023
Approval Date:	07 Sep 2023

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	20 Oct 2023
Original Protocol	07 Sep 2023

Amendment 1 (20 Oct 2023)

Overall Rationale for the Amendment:

The purpose of this protocol amendment was to update the criteria for discontinuation of the clinical study or study intervention, add standardized grading scales for the assessment of intensity of adverse events (AEs), and add text to state that all AEs / serious adverse events (SAEs) that occur during the study should be considered related to the study intervention unless there is another obvious etiology for the event.

Section Number (Heading Name)	Description of Change	Brief Rationale
Section 7.1 (Discontinuation of Study Intervention)	Changed the criteria for discontinuation of the clinical study or study intervention. Text was also deleted that stated that depending upon the nature of the event, a decision may be made by the sponsor to resume dosing, to proceed into the next cohort at a lower dose level, or to stop the study.	The criteria for discontinuation of the clinical study or study intervention were revised to specify the number and type of AEs that would trigger stopping of the clinical study or dose escalation.
Section 8.3.2 (Vital Signs)	Added text referring to Section 10.5 for guidance on how to assess vital signs with regards to AE intensity.	Updated as per guidance added to Section 10.3.4 and Section 10.5.
Section 8.3.4 (Clinical Safety Laboratory Tests)	Added text referring to Section 10.5 for guidance on how to assess clinical laboratory parameters with regards to AE intensity.	Updated as per guidance added to Section 10.3.4 and Section 10.5.
Section 8.4 (Adverse Events, Serious Adverse Events, and Other Safety Reporting)	Added text so state that VIS954 is a new investigational drug being investigated in healthy volunteers, AEs and SAEs should be considered related to study intervention unless there is another obvious etiology for the event.	Added this clarification regarding the relatedness to study intervention since the toxicity profile of VIS954 has not been characterized in humans.
Section 10.2 (Clinical Safety Laboratory Tests)	Added text referring to Section 10.5 for guidance on how to assess clinical laboratory parameters with regards to AE intensity.	Updated as per guidance added to Section 10.3.4 and Section 10.5.

Section Number (Heading Name)	Description of Change	Brief Rationale
Section 10.3.4 (Recording and Follow-up of AE and/or SAE)	Assessment of Intensity Added that the intensity of AEs and SAEs will be assessed per the standardized grading scale (Food and Drug Administration [FDA] Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, Sep 2007).	Added the FDA standardized grading scale so that the assessment of intensity is based on a standardized grading scale appropriate to healthy participants.
Section 10.3.4 (Recording and Follow-up of AE and/or SAE)	Assessment of Relatedness to Study Intervention Added text to state that as VIS954 is a new investigational drug being investigated in healthy volunteers, AEs and SAEs should be considered related to study intervention unless there is another obvious etiology for the event.	Added this clarification regarding the relatedness to study intervention since the toxicity profile of VIS954 has not been characterized in humans.
Section 10.5 - Appendix 5 (Adverse Event Intensity Assessment)	Updated the table for injection site assessment for consistency with the FDA standardized grading scale. Added the FDA standardized grading scale tables for AE intensity assessment for vital signs, clinical laboratory tests, systemic (general), and systemic (illness).	Added the FDA standardized grading scales so that the assessment of intensity is based on a standardized grading scale appropriate to healthy participants.

Additional Risk to the Subject:

There is no additional risk to the subjects.

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List of Abbreviations

Abbreviation	Definition
CCI	[redacted]
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
CCI	[redacted]
AST	Aspartate aminotransferase
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from predose extrapolated to infinite time
$AUC_{0\text{-last}}$	Area under the concentration-time curve from predose to the last quantifiable concentration
AxMP	Auxiliary medicinal product
β-hCG	Beta-human chorionic gonadotropin
C5aR1	Complement 5a receptor 1
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent clearance
C_{max}	Maximum serum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	Case report form
D	Day
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
Fc	Fragment crystallizable
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
hC5aR1	Human C5aR1
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgG4	Immunoglobulin G4
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRE	Immediately reportable event
KI	Knock-in

Abbreviation	Definition
MABEL	Minimal anticipated biological effect level
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
MPO	Myeloperoxidase
NA	Not applicable
NIMP	Noninvestigational medicinal product
NOAEL	No observed adverse-effect level
NSAID	Nonsteroidal anti-inflammatory drug
pC5a	Porcine C5a
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR3	Proteinase 3
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
RO	Receptor occupancy
RT-PCR	Reverse transcription polymerase chain reaction
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SMC	Safety monitoring committee
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Apparent terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum serum concentration
ULN	Upper limit of normal
V_d/F	Apparent volume of distribution

1 Protocol Summary

1.1 Synopsis

Protocol Title: A phase 1, randomized, placebo-controlled, double-blind, single ascending dose, first-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of VIS954 in healthy male and female participants.

Brief Title: A study to investigate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of VIS954 in healthy adult participants.

IND Number: 160,895

Rationale: This first-in-human (FIH) study will assess the safety, tolerability, PK, and PD of VIS954, an anti-complement 5a receptor 1 (C5aR1) monoclonal antibody. The results of the study will inform the design and dose selection of subsequent studies. The sponsor intends to develop VIS954 for the treatment of complement C5a mediated diseases CCI [redacted]

Objectives and Endpoints: The objectives and endpoints are summarized in the table below.

Objectives	Endpoints
Primary: • To evaluate the safety and tolerability of VIS954 in healthy participants	Primary: *Safety* The following safety variables will be assessed: • Incidence of TEAEs • Physical examinations • Vital sign measurements (blood pressure, pulse, body temperature, and respiratory rate) • 12-Lead ECGs • Clinical safety laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis) • Injection site reactions and Wong-Baker FACES Pain Rating Scale
Secondary: • To assess the PK profile of VIS954 • To determine the PD effect of VIS954 • CCI [redacted]	Secondary: *Pharmacokinetics* The following PK parameters for VIS954 will be determined, as appropriate: • C_{max} • t_{max} • $AUC_{0\text{-}inf}$ • $AUC_{0\text{-}last}$

Objectives	Endpoints
	• $t_{1/2}$ • V_d/F • CL/F *Pharmacodynamics* • To characterize VIS954 C5aR1 RO (VIS954 binding)
CCI	

CCI ; $AUC_{0\text{-inf}}$ = area under the concentration-time curve from predose extrapolated to infinite time; $AUC_{0\text{-last}}$ = area under the concentration-time curve from predose to the last quantifiable concentration; CL/F = apparent clearance; C_{max} = maximum serum concentration; ECG = electrocardiogram; RO = receptor occupancy; $t_{1/2}$ = apparent terminal elimination half-life; SC = subcutaneous; TEAEs = treatment-emergent adverse events; t_{max} = time of maximum serum concentration; V_d/F = apparent volume of distribution.

Overall Design Synopsis:

This is a phase 1, randomized, placebo-controlled, double-blind, single ascending dose, first-in-human (FIH) study to assess the safety, tolerability, PK, and PD of VIS954 administered subcutaneously (SC) in healthy participants.

The study will be conducted in 6 sequential cohorts. Each cohort will enroll 9 participants, randomized to VIS954 or placebo at a ratio of 7:2 (7 VIS954:2 placebo). Each cohort will also optimally enroll 5 non-Japanese participants and 4 Japanese participants (achievement of this ratio is desired but not mandatory to advance to the next cohort). No more than one Japanese participant per cohort may be randomized to receive placebo.

Potential participants will be carefully screened for eligibility prior to study enrollment.

On Day 1, a single dose of VIS954 or placebo will be administered SC.

Sentinel participants will be utilized in each cohort; the first 2 non-Japanese participants in each cohort will be randomized to receive either VIS954 (n = 1) or placebo (n = 1) and will receive the study intervention at least 24 hours before the remaining 7 participants in the cohort are dosed. The safety data from each of the 2 sentinel participants will be reviewed over the 24-hour postadministration period to determine whether it is

appropriate to proceed with dosing of the remaining participants in the cohort as planned. A similar review will occur for each dose escalation. The remaining 7 participants in a cohort will be randomized to receive VIS954 (n = 6) or placebo (n = 1).

Escalation to next dosing level will occur after review of blinded safety data when at least 7 participants have completed ≥ 14 days in a cohort.

The planned dose of VIS954 for each cohort is summarized in the table below.

Study Intervention for Each Cohort		
Cohort	**Study Intervention**	
Cohort 1	CCI	VIS954 or placebo
Cohort 2		VIS954 or placebo
Cohort 3		VIS954 or placebo
Cohort 4		VIS954 or placebo
Cohort 5		VIS954 or placebo
Cohort 6		VIS954 or placebo

Brief Summary:

This FIH study will assess the safety, tolerability, PK, and PD of VIS954.

The study is comprised of:

- A screening visit up to 28 days before dosing
- An in-house stay for 4 days, with admission to the study center on Day −1, SC administration on Day 1, and discharge on Day 3
- A postdose period with outpatient visits on Days 5 (± 2 days), 8 (+ 1 day), 11 (± 1 day), 15, 22, 29, 36, 43, and 57 (for all visits not otherwise specified, ± 3 days)
- A final follow-up visit on Day 71 (± 3 days)

Number of Participants:

Enrollment of approximately 54 participants is planned for this clinical study. Optimally, each cohort of 9 participants will include 5 non-Japanese participants and 4 Japanese participants (this ratio is desired but not mandatory).

Note: *Enrolled* means participants, or their legally acceptable representatives, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed

consent is not withdrawn prior to participating in any study activity after screening and if they are deemed eligible during the screening period.

Study Duration:

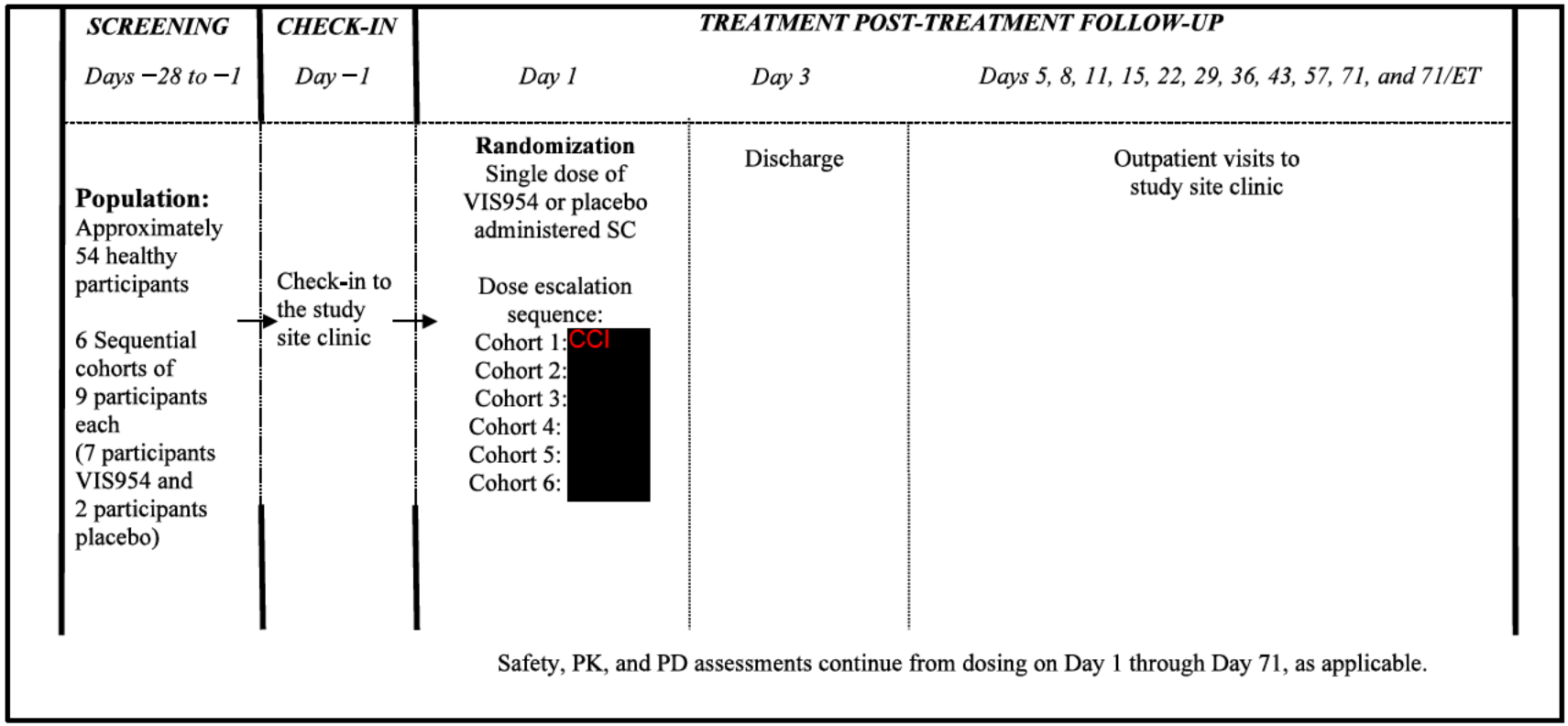
The total duration of the clinical study per participant will be up to 102 days (approximately 4 months), including the screening period.

Data Monitoring/Other Committee:

A safety monitoring committee (SMC) will be established for this study. When at least 7 participants have completed ≥ 14 days in a cohort, a review of the safety data will be performed by the SMC to authorize opening of the next cohort. The details of the SMC structure and its roles and responsibilities will be documented in the SMC charter.

1.2 Schema

Figure 1.2-1 Study Design Schematic



1.3 Schedule of Activities

Table 1.3-1 Schedule of Assessments

Activity	Screen	Base line		Treatment and Post-treatment Follow-up											
Time Point (Day)	**D −28 to D −1**	**D −1**	**D 1**	**D 2**	**D 3**	**D5**	**D 8**	**D11**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 57**	**D 71 /ET[a]**
± Visit Allowance	**NA**	**NA**	**NA**	**NA**	**NA**	**± 1**	**+ 1**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
In-house Stay		X	X	X	X										
Ambulatory Visit	X					X	X	X	X	X	X	X	X	X	X
PROCEDURES															
Informed Consent	X														
Verify Inclusion/ Exclusion Criteria	X	X													
Demographics and Medical History	X														
Pregnancy Test (serum β-hCG)[b]	X														
Pregnancy Test (urine dipstick)[b]		X													X
FSH[c]	X														
Viral Serology	X														
Urine Drug and Alcohol Screen	X	X													
Full Physical Examination[d]	X	X	X[e]	X	X										X
Brief Physical Examination[d]							X	X	X						
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X		X											
Review of Concomitant Medications	X														
Adverse Events Check	X														
Randomization			X												
Subcutaneous Injection			X												
Assessment of Injection Site[g]			X	X	X						X				

Table 1.3-1 Schedule of Assessments

Activity	Screen	Base line		Treatment and Post-treatment Follow-up										
Time Point (Day)	**D −28 to D −1**	**D −1**	**D 1**	**D 2**	**D 3**	**D5**	**D 8**	**D11**	**D 15**	**D 22**	**D 29**	**D 36**	**D 43**	**D 57**	**D 71 /ET[a]**
± Visit Allowance	**NA**	**NA**	**NA**	**NA**	**NA**	**± 1**	**+ 1**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Wong-Baker FACES Pain Rating Scale[g]			X	X	X						X				
LABORATORY ASSESSMENTS															
Hematology	X	X		X[h]	X				X		X			X	X
Serum Chemistry and Coagulation	X	X		X[h]	X				X		X			X	X
Urinalysis	X	X		X[h]	X				X		X			X	X
Blood Sampling for PK[i, j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PD (RO)		X		X[h]	X	X	X	X	X	X	X	X	X		X
Blood Sampling for PD (total leukocytes)[k]		X		X[h]			X		X						
CCI															

β-hCG = Beta-human chorionic gonadotropin; D = day; ET =early termination; FSH = follicle stimulating hormone.
Note: Unless otherwise stated, the window allowance for all assessment time points are ± 15 minutes.

[a]If a participant discontinues from the study, the assessments of the Day 71 visit will be performed at the ET visit.

[b]Limited to participants of childbearing potential.

[c]Limited to participants in whom nonchildbearing potential needs validation or per trial site standard operating procedure.

[d]The full physical examination will include, at a minimum, assessment of general appearance and an evaluation of skin, head, eyes (excluding fundoscopic examination of retinae), ears, nose and throat, chest and abdomen (excluding rectal examination), extremities, and musculoskeletal system. The brief physical examination will include, at a minimum, assessment of the general appearance, skin, cardiovascular system, respiratory system, and abdomen.

[e]The full physical examination on Day 1 will be performed at approximately 2 hours postdose (± 1 hour window).

[f]Vital signs will include blood pressure, pulse, body temperature, and respiratory rate. Height and weight will also be measured at screening. Vital signs measurements will be recorded on Day 1 within 30 minutes predose and at 2 and 4 hours postdose. At subsequent time points, vital signs will be recorded at approximately the same time of day, if possible and/or convenient.

[g]The investigator or trained, qualified designee will assess the injection site for local tolerability at 1 and 4 hours postdose (Day 1), 24 hours postdose (Day 2), and on Days 3 and 29. Participants will also assess the pain associated with the injection using the Wong-Baker FACES Pain Rating Scale at the same time points.

[h]Samples to be collected at 24 hours following the injection on Day 1.

[i]Blood samples for PK analysis will be collected on Day 1 (within 2 hours predose [± 1 hour], 4 hours postdose [± 1 hour], and 8 hours postdose [± 1 hour]), Day 2 (24 hours postdose [± 1 hour]), and Day 3 (48 hours postdose [± 1 hour]). All participants will also have blood samples collected for PK analysis on Days 5, 8, 11, 15, 22, 29, 36, 43, 57, and 71; there are no time points specified for the collection of PK blood samples on these days.

CCI [redacted]

[redacted]

2 Introduction

VIS954 is a humanized immunoglobulin (Ig) G4 monoclonal antibody and orthosteric, insurmountable antagonist of human complement 5a receptor 1 (hC5aR1). C5aR1 is the receptor for the complement fragment and anaphylotoxin, C5a. C5aR1 is expressed on myeloid cells, including neutrophils.[1,2,3] The sponsor intends to develop VIS954 for the treatment of complement C5a mediated diseases CCI [redacted]

2.1 Study Rationale

This first-in-human (FIH) study will assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of VIS954, an anti-C5aR1 monoclonal antibody. The results of the study will inform the design and dose selection of subsequent studies.

2.2 Background

CCI [redacted]

[redacted] C5aR1 is a class A G protein-coupled receptor that functions in the complement cascade. The binding of ligand C5a to C5aR1 is one of the terminal events in the complement pathway that can lead to the activation and transmigration of leukocytes, including neutrophils, and the release of inflammatory mediators.

The VIS954 mechanism of action is to reduce aberrant inflammation and tissue damage by blocking C5aR1 signaling and subsequent chemotaxis and activation of leukocytes to the site of inflammation. VIS954 specifically targets and binds to the site II region on C5aR1, blocking C5a binding to C5aR1. C5a binds to C5aR1 in a two-step process, first interacting with site I on the N-terminal domain of C5aR1, and then interacting with basic residue on site II located on the second extracellular loop of C5aR1. It is the

binding of C5a to site II of C5aR1 that initiates a signaling cascade. As a C5aR1 antagonist, VIS954 inhibits C5aR1-mediated signaling, and consequently, prevents the recruitment and activation of neutrophils by C5a. VIS954 is a fragment crystallizable (Fc)-silenced antibody as mutations were introduced to the Fc domain to reduce effector function, a known consequence of Fcγ receptors recognizing and binding the Fc region of IgG antibodies.

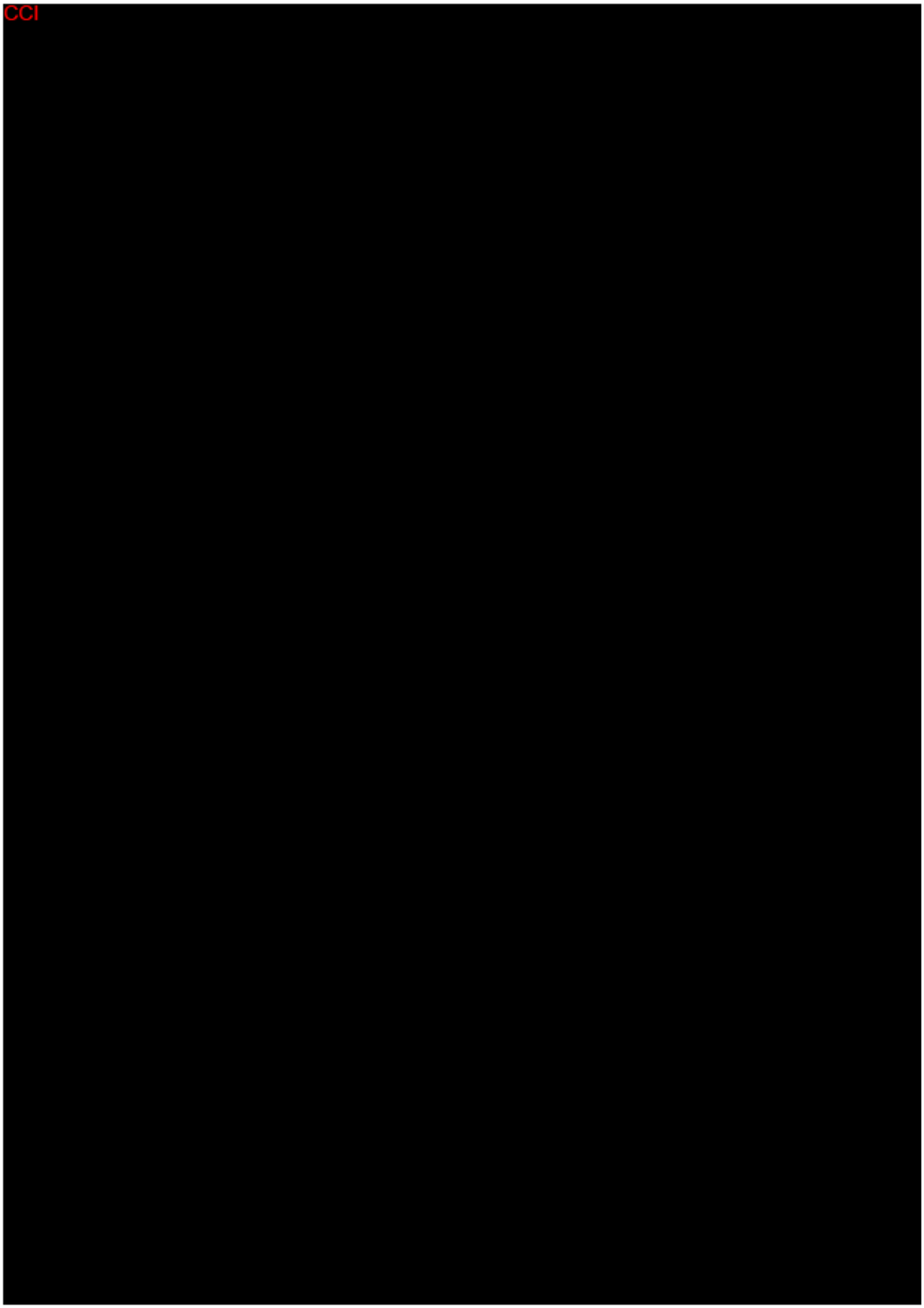
CCI [redacted]

A detailed description of VIS954 is provided in the Investigator's Brochure (IB).

CCI [redacted]

CCI

[redacted]


CCI


CCI

3 Objectives and Endpoints

The objectives and endpoints are summarized in Table 3-1.

Table 3-1 Objectives and Endpoints

Objectives	Endpoints
Primary: • To evaluate the safety and tolerability of VIS954 in healthy participants	Primary: *Safety* The following safety variables will be assessed: • Incidence of TEAEs • Physical examinations • Vital sign measurements (blood pressure, pulse, body temperature, and respiratory rate) • 12-Lead ECGs • Clinical safety laboratory tests (hematology, clinical chemistry, coagulation, and urinalysis) • Injection site reactions and Wong-Baker FACES Pain Rating Scale
Secondary: • To assess the PK profile of VIS954 • To determine the PD effect of VIS954 • CCI [redacted]	Secondary: *Pharmacokinetics* The following PK parameters for VIS954 will be determined, as appropriate: • C_{max} • t_{max} • $AUC_{0\text{-}inf}$ • $AUC_{0\text{-}last}$ • $t_{1/2}$ • V_d/F • CL/F *Pharmacodynamics* • To characterize VIS954 C5aR1 receptor occupancy (VIS954 binding)
CCI [redacted]	

CCI ; AUC_{0-inf} = area under the concentration-time curve from predose extrapolated to infinite time; AUC_{0-last} = area under the concentration-time curve from predose to the last quantifiable concentration; CL/F = apparent clearance; C_{max} = maximum serum concentration; $t_{1/2}$ = apparent terminal elimination half-life; TEAEs = treatment-emergent adverse events; t_{max} = time of maximum serum concentration; V_d/F = apparent volume of distribution.

4 Study Design

4.1 Overall Design

This is a phase 1, randomized, placebo-controlled, double-blind, single ascending dose, FIH study to assess the safety, tolerability, PK, and PD of VIS954 administered SC in healthy participants.

The study will be conducted in 6 sequential cohorts. Each cohort will enroll 9 participants, randomized to VIS954 or placebo at a ratio of 7:2 (7 VIS954:2 placebo). Each cohort will also optimally enroll 5 non-Japanese participants and 4 Japanese participants (achievement of this ratio is desired but not mandatory to advance to the next cohort). No more than one Japanese participant per cohort may be randomized to receive placebo.

The study is comprised of:

- A screening visit up to 28 days before dosing
- An in-house stay for 4 days, with admission to the study center on Day −1, SC administration on Day 1, and discharge on Day 3
- A postdose period with outpatient visits on Days 5 (± 2 days), 8 (+ 1 day), 11 (± 1 day), 15, 22, 29, 36, 43, and 57 (for all visits not otherwise specified, ± 3 days)
- A final follow-up visit on Day 71 (± 3 days)

The total duration of the clinical study per participant will be up to 102 days (approximately 4 months), including the screening period.

Potential participants will be carefully screened for eligibility prior to study enrollment.

On Day 1, a single dose of VIS954 or placebo will be administered SC.

Sentinel participants will be utilized in each cohort; the first 2 non-Japanese participants in each cohort will be randomized to receive either VIS954 (n = 1) or placebo (n = 1) and will receive the study intervention at least 24 hours before the remaining 7 participants in the cohort are dosed. The safety data from each of the 2 sentinel participants will be reviewed over the 24-hour postadministration period to determine whether it is appropriate to proceed with dosing of the remaining participants in the cohort as planned. A similar review will occur for each dose escalation. The remaining 7 participants in a cohort will be randomized to receive VIS954 (n = 6) or placebo (n = 1).

Escalation to next dosing level will occur after review of blinded safety data when at least 7 participants have completed ≥ 14 days in a cohort.

The planned dose of VIS954 for each cohort is summarized in Table 4.1-1.

Table 4.1-1 Study Intervention for Each Cohort

Cohort	Study Intervention
Cohort 1	CCI VIS954 or placebo
Cohort 2	VIS954 or placebo
Cohort 3	VIS954 or placebo
Cohort 4	VIS954 or placebo
Cohort 5	VIS954 or placebo
Cohort 6	VIS954 or placebo

4.2 Scientific Rationale for Study Design

The nonclinical pharmacology, PK, and toxicology profiles of VIS954 have been adequately characterized and support the evaluation of VIS954 in this FIH study.

The single ascending dose (SAD) design is considered appropriate to assess the safety, tolerability, PK, and PD of VIS954. Initial dosing in each cohort will be limited to 2 non-Japanese participants who will serve as 'sentinel participants'. Escalation to the next dosing level cohort will only occur after review of safety by the SMC when at least 7 participants have completed ≥ 14 days in a cohort.

The planned safety assessments are conventional, accepted measures for assessing the safety of participants during a clinical study. The PK and PD sampling schedule is based on the nonclinical PK and PD.

4.2.1 Patient Input into Design

Not applicable.

CCI

CCI

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed the last visit.

5 Study Population

The study population will consist of healthy non-Japanese and Japanese male and female participants. Participants must be able to provide written informed consent and meet all the inclusion criteria and none of the exclusion criteria.

Enrollment of approximately 54 participants is planned for this clinical study. Optimally, each cohort of 9 participants will include 5 non-Japanese participants and 4 Japanese participants (this ratio is desired but not mandatory).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female participant between 18 to 55 years of age, inclusive, at the screening visit.
2. Non-Japanese participant: Participant does not meet the criteria specified below for 'Japanese Participant'.
3. Japanese participant: Participant is of Japanese descent as evidenced by verbal confirmation of familial heritage (a participant's 4 grandparents were born in Japan and recognized to be 'Japanese').
4. Body mass index between 18.0 and 30.0 kg/m^2, inclusive, at the screening visit.
5. Total body weight between 50.0 and 120.0 kg, inclusive, at the screening visit.
6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and the protocol.
7. Willing and able to participate in the study for the defined duration of the study.
8. Female participants will be nonpregnant, nonlactating, and either postmenopausal for at least 1 year or surgically sterile for at least 3 months, or will agree to use highly effective methods of contraception from the period prior to study enrollment until 30 days after Day 56; women of childbearing potential must have a negative serum beta-human chorionic gonadotropin (β-hCG) test at screening and a negative urine pregnancy test at baseline prior to administration of the study intervention.

9. Male participants with female partners of childbearing potential must agree to use double barrier contraception or abstain from sex during the study and until 90 days after Day 56. Male participants must agree to refrain from sperm donation for the duration of the study and until 90 days after Day 56. This criterion may be waived for male participants who have had a vasectomy greater than 6 months prior to enrollment.
10. Healthy, as determined by prestudy medical evaluation (medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluations), as judged by the principal investigator.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant has a history or current evidence of a serious and/or unstable cardiovascular, respiratory, gastrointestinal, hematologic, autoimmune, blood dyscrasias or other medical disorder, including psychiatric disorders, cirrhosis, or malignancy. History of minor skin cancers (not including melanoma) or surgically treated, limited cervical carcinomas (ie, carcinoma in situ) are not exclusionary.
2. Participant is participating in another clinical study of any investigational drug, device, or intervention or has received any investigational medication during the last 30 days or 5 half-lives, whichever is longer, before baseline (Day −1).
3. Previous receipt of antibody or biologic therapy.
4. History of a previous hypersensitivity or severe allergic reaction with generalized urticaria, angioedema, or anaphylaxis to any of the ingredients of the VIS954 SC injection formulation.
5. Blood pressure > 160/100 mmHg or < 90/50 mmHg (may be repeated once if abnormal), at the screening visit or Day −1.
6. History of any infection requiring hospitalization or treatment with antivirals, antibiotics, or systemic antifungals within 3 months prior to screening.
7. Received a vaccination, other than COVID-19 vaccination, during the 30 days prior to administration of the first dose of study intervention. A COVID-19 vaccination cannot be received within 7 days prior to the first dose of study intervention and until 14 days after the last dose.

8. Has received any prescription or nonprescription (over-the-counter) medication during the last 30 days or 5 half-lives, whichever is longer, preceding baseline (Day −1), with the exception of acetaminophen, ibuprofen, naproxen (or other over-the-counter nonsteroidal anti-inflammatory drugs [NSAID]), hormonal contraceptives, topical medications, vitamins, and dietary or herbal remedies.
9. Any participant who has a recent history of alcohol or drug/chemical abuse, at the discretion of the investigator, will be excluded.
10. Enrolled participants must abstain from consumption of nicotine containing products from Day −1 through discharge.
11. Enrolled participants must abstain from consumption of cannabinoids from Day−1 through end of study.
12. For the duration of the study, enrolled male participants should not consume more than 15 standard drinks per week (7 days) and female participants should not consume more than 10 standard drinks per week (7 days). A standard drink equals 10 g of alcohol. Enrolled participants must abstain from consuming alcohol 48 hours prior to check-in on Day −1 through discharge.
13. Participant with a positive urine drug or alcohol breath screen test result at screening or Day −1. The urine drug screen and alcohol breath screen may be repeated once at the discretion of the investigator. The urine drug screen also screens for methylenedioxymethamphetamine and propoxyphene. If a participant tests positive on these tests, inclusion of that participant into the study will be based on the principal investigator's judgment with consultation, as needed, with the medical monitor and the sponsor.
14. Any chronic infectious disease (eg, chronic urinary tract infection, chronic sinusitis, bronchiectasis, active pulmonary or systemic tuberculosis [TB], chronic viral hepatitis such as hepatitis C or hepatitis B, or human immunodeficiency virus [HIV] infection).
15. Participant who has donated > 500 mL of blood within 60 days prior to start of the screening visit or the participant has donated any plasma within 7 days prior to baseline (Day −1).
16. Coronavirus disease 2019:
    - Current symptoms of infection.
    - Diagnosis of COVID-19 (reverse transcription polymerase chain reaction [RT-PCR], antigen testing, or clinical diagnosis) in the 21 days prior to screening.
    - Ongoing diagnosis of "Long-COVID" symptoms, due to a prior COVID-19 infection.

17. Is an employee of the clinical research team (any sponsor or research site employee), or has a family member who is an employee of these organizations.
18. Participant is judged by the investigator or the medical monitor to be inappropriate for the study.

5.2.1 Meals and Dietary Restrictions

There are no meal or dietary restrictions.

5.2.2 Caffeine, Alcohol, and Tobacco

5.2.2.1 Caffeine

There are no restrictions on caffeine.

5.2.2.2 Alcohol

For the duration of the study, male participants should not consume more than 15 standard alcohol drinks per week (7 days) and female participants should not consume more than 10 standard alcohol drinks per week (7 days). A standard drink equals 10 g of alcohol.

Enrolled participants must abstain from consuming alcohol 48 hours prior to check-in to the study site on Day −1 through discharge.

5.2.2.3 Tobacco

Enrolled participants must abstain from consumption of nicotine containing products and cannabinoids while admitted to the study site (Day−1 through discharge).

5.2.2.4 Cannabinoids

Enrolled participants must abstain from consumption of cannabinoids from Day−1 through end of the study.

5.2.3 Activity

There are no restrictions on activity.

5.2.4 Other Restrictions

Blood donation (> 500 mL) is prohibited within 60 days prior to start of screening and/or donation of any plasma within 7 days prior to baseline (Day −1). Blood and plasma donation is also prohibited for the duration of the study and for 30 days after the last dose of study intervention.

5.3 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.4 Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention

Not applicable.

6 Study Interventions and Concomitant Therapy

Study interventions are all pre-specified, investigational and noninvestigational medicinal products, medical devices, or other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention Administered

On Day 1, participants will receive a single fixed SC dose of study intervention (VIS954 or placebo), either as 1 or 2 injections.

A summary of the study interventions to be administered during this study is provided in Table 6.1-1.

Table 6.1-1 Study Intervention(s) Administered

Intervention Name	VIS954	Placebo
Intervention Description	Administered on Day 1 as a single fixed dose	Administered on Day 1
Type	Drug	Drug
Dose Formulation	Solution	Solution
Unit Dose Strength(s)	Fixed dose	NA
Dosage Levels	CCI [redacted]	Not applicable
Route of Administration	SC	SC
Use	Experimental	Placebo comparator
IMP and NIMP/AxMP.	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	The study intervention will be provided as vials and labeled according to applicable local and regulatory requirements.	

AxMP = auxiliary medicinal product; IMP = investigational medicinal product; NA = not applicable; NIMP = noninvestigational medicinal product.

6.2 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The study intervention will be supplied in vials. The study pharmacist (or designee) will dispense study intervention for each participant according to the protocol and pharmacy manual.

Prior to administration, the study intervention should be placed at room temperature to allow for temperature equilibration. For further details on drug preparation and administration, please refer to the pharmacy manual.

The investigator or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All dispensing and accountability records will be available for sponsor review. When the study monitor visits the study site, he/she will reconcile the drug accountability log with the products stored in the pharmacy.

Further guidance and information for the final disposition of unused study interventions are provided in the study reference manual.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention. Before the study is initiated, information and directions for the randomization will be provided to the trial site.

6.4 Blinding

This is a double-blind study in which participants, investigators, other study site staff, and certain members of the sponsor (as described in the operations manual) are blinded to study intervention. An unblinded pharmacist (or other unblinded designee) will prepare the study intervention doses for SC administration.

Prior to activation for screening, the trial site will be provided with emergency blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact the sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.5 Study Intervention Compliance

Preparation of individual doses of study intervention will be verified by a second (unblinded) member of the study site pharmacy staff.

Participants will be dosed at the study site and they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose Modification

The sponsor's unblinded Clinical Pharmacology team members may provide dose modification recommendations (either a decrease, increase, or repeat of the previous dose) to the SMC in the event of any observed deviations from the predicted dosing regimen / modeling.

6.6.1 Retreatment Criteria

Not applicable.

6.7 Continued Access to Study Intervention after the End of the Study

Not applicable; there will be no access to the study intervention following the end of the study.

6.8 Treatment of Overdose

Standard symptomatic measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and clinical laboratory abnormalities until the last visit or until the AE/SAE has resolved.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and Concomitant Therapy

Prior and concomitant medication use is not permitted during the last 30 days preceding baseline (Day −1) until end of study (including over-the-counter and prescription

medicines, except for acetaminophen, ibuprofen [or an equivalent NSAID], naproxen, hormonal contraceptives, topical medications, vitamins, and dietary or herbal remedies). However, concomitant medication use may be warranted for the treatment of AEs. The use of concomitant medications to treat AEs should be discussed between the investigator and the medical monitor.

6.9.1 Rescue Medicine

Not applicable.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Dose escalation will be stopped if the dose for a cohort is determined not to be safe or well tolerated. Specifically, the clinical study and dose escalation will be stopped if participants who received study intervention meet any of the following criteria:

- One SAE (unless the SAE is clearly not related to the study intervention, eg, a motor vehicle accident or clear alternative etiologies).
- Two participants experience a severe AE (Grade 3) or one participant experiences a potentially life-threatening AE (Grade 4) as per the standardized grading scale (Food and Drug Administration [FDA] Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, Sep 2007).[12]

7.1.1 Temporary Discontinuation

Not applicable.

7.1.2 Rechallenge

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason). This is expected to be uncommon. Every effort will be made to determine why any participant withdraws from the study prematurely.

All participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study site records.

Participants may withdraw or be withdrawn from study for the following reasons:

- Withdrawal of consent
- Adverse event
- Protocol deviation

- Investigator decision
- Pregnancy
- Loss to follow-up
- Sponsor decision to terminate the study
- Other

Participants can be replaced at the discretion of the sponsor. The same treatment will be allocated to the replacement participant.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Assessments (Table 1.3-1).

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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, 3 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.

Discontinuation of the study as a whole are handled as part of Section 10.1.10.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Assessments (Table 1.3-1). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the Schedule of Assessments.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL per month.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

Demographics and medical history will be collected at screening as described in the Schedule of Assessments (Table 1.3-1).

8.2 Efficacy Assessments

Not applicable.

8.3 Safety Assessments

8.3.1 Physical Examinations

Physical examinations will be performed at the time points summarized in the Schedule of Assessments (Table 1.3-1).

A full physical examination will include, at a minimum, assessment of general appearance and an evaluation of skin, head, eyes (excluding fundoscopic examination of

retinae), ears, nose and throat, chest and abdomen (excluding rectal examination), extremities, and musculoskeletal system.

A brief physical examination will include, at a minimum, assessment of the general appearance, skin, cardiovascular system, respiratory system, and abdomen.

8.3.2 Vital Signs

Vital sign assessments will be performed at the time points summarized in the Schedule of Assessments (Table 1.3-1). Blood pressure will be performed in triplicate at screening and as a single measurement at all other time points.

Vital signs including blood pressure, heart rate, respiratory rate, and temperature will be assessed. Height (at screening only) and weight will also be measured.

Blood pressure and pulse measurements will be assessed while the participant is seated or supine with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (no television, cell phone, etc).

Whenever possible, vital signs should be collected before blood collection for laboratory tests and before dosing with study intervention.

Please see Section 10.5 for guidance on how to assess vital signs with regards to AE intensity.

8.3.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the Schedule of Assessments (Table 1.3-1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT interval corrected for heart rate using Fridericia's formula (QTcF) intervals.

Twelve-lead ECGs should be conducted after 5 minutes in recumbence or semi-recumbency.

The investigator may repeat or perform an ECG at any time if medically necessary.

8.3.4 Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests (hematology, serum chemistry, coagulation, and urinalysis) to be performed and the Schedule of Assessments (Table 1.3-1) for the timing and frequency.

An investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by an investigator or medical monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual.

If laboratory values from nonprotocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded on the case report form (CRF) or in the electronic case report form (eCRF).

Please see Section 10.5 for guidance on how to assess clinical laboratory parameters with regards to AE intensity.

8.3.5 Pregnancy Testing

Pregnancy tests will be performed at the time points summarized in the Schedule of Assessments (Table 1.3-1).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Assessment of Injection Site

Assessment of the injection site will be performed at the time points summarized in the Schedule of Assessments (Table 1.3-1).

Poor local tolerability is defined as an injection site reaction deemed abnormal from those ordinarily observed for subcutaneous injections (including a large erythematous reaction, induration, significant pain, itching, or swelling).

The injection site should be observed and evaluated by the blinded (as applicable) investigator or trained, qualified designee. If a reaction is observed, it will be graded on a

4-point categorical scale (Mild, Moderate, Severe, Potentially Life-threatening) for the presence or absence of any of the clinical features described per the scale in Section 10.5.

Whenever possible, the same individual should perform all assessments of the injection site for any participant.

8.3.7 Wong-Baker FACES Pain Rating Scale

Participants will assess the pain associated with the injection using a validated pain scale, the Wong-Baker FACES Pain Rating Scale at the time points summarized in the Schedule of Assessments (Table 1.3-1).

The Wong-Baker FACES Pain Rating Scale is a subjective self-report that will used to record each participant's perception of pain associated with their injection. The level of pain will be recorded along with any further assessment.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs, SAEs, and immediately reportable events (IREs) can be found in Section 10.3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting IRE reports are provided in Section 10.3. VIS954 is a new investigational drug being investigated in healthy volunteers, AEs and SAEs should be considered related to study intervention unless there is another obvious etiology for the event. The contact for IRE reporting is provided in Section 10.3.6.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last visit as specified in the Schedule of Assessments (Table 1.3-1).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History / Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

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

8.4.3 Follow-up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits and/or contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate, according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 30 days after Day 56 (female participants) or 90 days after Day 56 (female partners of male participants).

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor. Infants will be followed for a minimum of 6 months from the date of birth.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Adverse Events of Special Interest

Not applicable.

8.4.8 Potential Serious Hepatotoxicity

For a participant who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE in the CRF/eCRF.

8.4.9 Medical Device Deficiencies

Not applicable.

8.5 Pharmacokinetics

Whole blood samples will be collected for measurement of serum concentrations of VIS954 at the time points specified in the Schedule of Assessments (Table 1.3-1).

CCI [redacted]

Instructions for the collection and handling of biological samples will be provided by the sponsor in a separate laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 Pharmacodynamics

To characterize the effect of VIS954 on C5aR1 RO (VIS954 binding), whole blood samples will be collected at the time points specified in the Schedule of Assessments (Table 1.3-1).

Instructions for the collection and handling of biological samples will be provided by the sponsor in a separate laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

CCI [redacted]

CCI

[redacted]

8.7 Genetics

Not applicable.

CCI

[redacted]

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to VIS954.

8.10 Health Economics or Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical Considerations

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

In general, descriptive statistics for continuous variables will be summarized by treatment group using number of participants, arithmetic mean, standard deviation, median, minimum and maximum; descriptive statistics for categorical data will be summarized by treatment group using frequency counts and percentages. The placebo participants will be pooled into a single placebo group for summaries and presentations. Therefore, treatment group will refer to each of the dose level of VIS954 and pooled placebo.

Adverse events, clinical laboratory tests, vital sign measurements, ECGs, physical examinations, and injection site reactions are the primary endpoints of the study. All AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

The incidence of TEAEs will be summarized by treatment group.

Participants with clinically significant abnormalities in clinical laboratory tests, vital signs, physical examinations, and injection site reactions will be summarized by count and percentage.

In general, missing data will be left missing, analyses will be conducted based on the available cases and will be clearly reflected by reporting a category of "NOT REPORTED" or reflected in the total number of participants used for analysis.

9.1 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- Screened analysis set: All participants who sign the ICF.
- Randomized Analysis Set: Participants who are randomized.
- Safety analysis set: All participants exposed to study intervention.
- Pharmacokinetic Analysis Set: All screened participants who receive study intervention and have at least 1 evaluable postdose VIS954 serum concentration.
- Pharmacodynamic Analysis Set: All screened participants who receive study intervention and have at least one evaluable PD measure.
- CCI [redacted]

9.2 Statistical Analyses

9.2.1 General Considerations

All data collected will be documented using summary tables, figures, and/or participant data listings presented by treatment group and dose group.

Data grouped by treatment group and overall will be analyzed separately if deemed appropriate, details will be described in the statistical analysis plan (SAP).

9.2.2 Safety Analysis

9.2.2.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed.

The incidence of the following events will be summarized:

- TEAEs
- TEAEs by severity
- Serious TEAEs
- TEAEs leading to discontinuation of the study intervention
- Serious TEAEs leading to discontinuation of the study intervention

The categories of the relationship to study intervention will be summarized as related and not related.

9.2.2.2 Clinical Laboratory Data

Individual data listings of laboratory results will be presented for each participant. Flags will be attached to values outside of the laboratory's reference limits along with the principal investigator's assessment. Clinically significant laboratory test abnormalities that were considered AEs by the principal investigator will be presented in the AE listings.

Clinical laboratory tests (observed values) will be summarized using descriptive statistics. Shift tables will be presented for select laboratory parameters.

9.2.2.3 Physical Examination and Vital Signs Data

Physical examination data will be provided in a data listing.

Individual data listings of vital signs (observed and change from baseline) will be presented for each participant. Individual clinically significant vital signs findings that were considered AEs by the principal investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized using descriptive statistics.

9.2.2.4 Electrocardiogram Data

Standard 12-lead ECG results will be listed for each participant. Descriptive statistics will be calculated for ECG parameters. The incidence of abnormalities, based on the clinical interpretations from the principal investigator, will be summarized.

9.2.2.5 Assessment of Injection Site

Data for the assessment of the injection site will be summarized using descriptive statistics.

9.2.2.6 Wong-Baker FACES Pain Rating Scale

Data for the Wong-Baker FACES Pain Rating Scale scores for pain perception will be summarized using descriptive statistics.

9.2.3 Pharmacokinetic Analysis

Pharmacokinetic samples will be used for the analysis of VIS954. The PK parameters will be determined by a noncompartmental analysis of serum concentrations for VIS954. No inferential statistical analyses will be performed. In general, PK data will be summarized by treatment group for non-Japanese, Japanese, and all participants using descriptive statistics and listed by participant (as applicable). Individual and summary tables using descriptive statistics (N, median, mean, standard deviation, percent coefficient of variation, minimum, and maximum) will be presented for serum concentrations and PK parameters. The individual, mean, and median plots of serum concentrations will also be provided.

9.2.4 Pharmacodynamic Analysis

Pharmacodynamic parameters will be summarized using descriptive statistics and plotted over time, as applicable. Baseline data will be taken as the last measurement prior to dosing or if not available, the screening value will be used instead.

9.2.5 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

9.2.6 Other Endpoint Analysis

CCI

[redacted]

9.2.7 Other Analyses

9.2.7.1 Disposition of Participants

Participants excluded from the analysis sets and data excluded from the PK and PD analysis will be listed including the reason for exclusion. Participant disposition will be summarized. Disposition data will be presented based on all participants randomized.

9.2.7.2 Protocol Deviations

Protocol deviations will be listed by participant.

9.2.7.3 Analysis of Demographic and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight, and body mass index) will be listed for each participant. Demographic characteristics (age, sex, ethnicity, and race) and anthropometric characteristics (height, weight, and body mass index) will be summarized by treatment group and for all participants in the safety population.

Medical history data will be listed for each participant including visit, description of the disease/procedure, MedDRA system organ class, MedDRA preferred term, start date, and stop date (or ongoing if applicable).

9.2.7.4 Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the dose of study intervention. Concomitant medications are those taken after the first dose (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed for each participant and will include the following information: reported name, preferred term, the route of administration, dose, frequency, start date/time, duration, and indication.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary.

9.2.7.5 Study Intervention Administration

A listing of study intervention administration will be created and will include the date and time of administration. When appropriate, a summary table of compliance will also be created.

9.3 Interim Analyses

A SMC will be established for this study. When at least 7 participants have completed ≥ 14 days in a cohort, a review of the safety data will be performed by the SMC to authorize opening of the next cohort. There will be no formal statistical comparison for the SMC meeting.

Interim summaries of data may be utilized by unblinded members of the sponsor (as described in the operations manual) for various reporting and future study planning purposes at any time prior to full database lock.

9.4 Sample Size Determination

The sample size for this FIH study was not based on formal statistical determinations. The sample size for this study was chosen in consideration of limiting exposure to this new chemical entity while providing sufficient information to evaluate the safety and tolerability of VIS954 in a phase 1 setting.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Any protocol change that significantly affects the safety of participants shall be submitted to the applicable regulatory authority according to local regulations. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately provided the regulatory authority is subsequently notified.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator or the investigator's representative will explain orally and in writing the nature, duration, and purpose of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant. The principal investigator will retain a copy as part of the clinical study records. The terms of the consent and when it was obtained must also be documented.

Participants who are rescreened are required to sign a new ICF.

The ICF will detail optional exploratory research to the participants, including the retention of remaining mandatory samples. This will include the type of biological material being stored and the potential objectives for exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4 Recruitment Strategy

A participant recruitment plan may be developed and implemented to assist study sites with their overall recruitment efforts for the study.

10.1.5 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5.1 Participant Identification

All screened participants are assigned a unique screening number. The screening numbers identify participants from time of screening until time of enrollment. Participants who drop out of the clinical study before enrollment will retain their screening numbers.

10.1.6 Safety Monitoring Committee

The details of the SMC structure and its roles and responsibilities will be documented in the SMC charter.

When at least 7 participants have completed ≥ 14 days in a cohort, a review of the safety data will be performed by the SMC to authorize opening of the next cohort, as described in Section 4.1.

10.1.7 Dissemination of Clinical Study Data

Dissemination of clinical study data will be per local regulations and sponsor operating procedures.

10.1.8 Data Quality Assurance

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The monitoring of the study will be conducted under the responsibility of the sponsor by the clinical research organization. The monitor will perform on-site and/or remote monitoring visits as frequently as necessary per the individual study monitoring plan.

The principal investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the study site and the sponsor is essential to ensure that the safety of the study is monitored adequately. the principal investigator will make all appropriate safety assessments on an ongoing basis. The medical monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures for compliance with applicable government regulations.

The study monitor will be an authorized individual designated by the sponsor. The study monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the principal investigator.

The sponsor will be entitled to audit the facilities used in the clinical and laboratory parts of the study, as well as to access all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of the national GCP compliance program or to review the results of this study in support of a regulatory submission.

The principal investigator should immediately notify the sponsor if they have been contacted by a regulatory/ethics agency concerning an inspection.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

First Act of Recruitment

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

The first act of recruitment is opening of the study site and will be the study start date.

Study/Site Termination

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 reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any contract research organization(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.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit the final draft of all manuscripts or abstracts to the sponsor at least 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments.

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.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 10.2-1 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	Basophils (percentage and absolute count)
	Eosinophils (percentage and absolute count)
	Hematocrit
	Hemoglobin
	Lymphocytes (percentage and absolute count)
	Mean corpuscular hemoglobin
	Mean corpuscular hemoglobin concentration
	Mean corpuscular volume
	Monocytes (percentage and absolute count)
	Neutrophils (percentage and absolute count)
	Platelet count
	Red blood cell count
	Red blood cell distribution width
	White blood cell count
Serum Chemistry	Albumin
	Alkaline phosphatase
	ALT
	AST
	Calcium
	Chloride
	Total cholesterol
	Creatinine
	Gamma glutamyl transferase
	Glucose (fasting [8 hours])
	Lactate dehydrogenase
	Phosphorus
	Potassium
	Sodium
	Total bilirubin (if out of range, direct and indirect bilirubin will be measured)
	Total protein
	Triglycerides
	Uric acid

Table 10.2-1	Protocol-required Safety Laboratory Tests
Laboratory Tests	**Parameters**
Coagulation	Partial thromboplastin time
	Prothrombin time
	International normalized ratio
Urinalysis	Bilirubin
	Blood
	Creatinine
	Glucose
	Ketones
	Leukocytes
	Nitrite
	pH and specific gravity
	Protein
	Urobilinogen
	Microscopic (only for abnormal urine stick test findings)
Serology[a]	HBsAg
	HBcAb
	Hepatitis C virus antibody
	HIV enzyme-linked immunosorbent assay
Urine drug and alcohol screen	Alcohol
	Amphetamines
	Barbiturates
	Benzodiazepines
	Cannabinoids
	Cocaine
	Methylenedioxymethamphetamine
	Opiates
	Phencyclidine
	Propoxyphene
Pregnancy testing	Serum β-hCG / urine dip stick (participants of childbearing potential only)
Other	FSH (screening visit only, limited to female participants in whom nonchildbearing potential needs validation or per trial site standard operating procedure)

FSH = follicle stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; RNA = ribonucleic acid.

[a]Participants with positive HBsAg will be excluded. Participants with a positive HBcAb test must undergo testing for hepatitis B virus DNA; if hepatitis B virus DNA is undetectable, the participant can be included in the study. Participants with a positive anti-hepatitis C virus antibody test must undergo testing for hepatitis C virus RNA; if hepatitis C virus RNA is undetectable, the participant can be included in the study.

Please see Section 10.5 for guidance on how to assess clinical laboratory parameters with regards to AE intensity.

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by the participants will be collected during an interview with the participants and by review of available medical records at the next visit.

Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant.

Events Meeting the AE Definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

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

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

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

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* 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.

c. Requires inpatient 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.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3 Definition of Immediately Reportable Event

- Any SAE
- Any AE related to occupational exposure
- Potential serious hepatotoxicity (see Section 8.4.8)
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate study intervention discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. This includes pregnancy of the participant or the partner of the participant. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female participant and there is an abnormality or complication.

10.3.4 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to IQVIA in lieu of completion of the required form.

There may be instances when copies of medical records for certain cases are requested by IQVIA. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to IQVIA.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories per the standardized grading scale (FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, Sep 2007):[12]

- Mild (Grade 1):
  A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate (Grade 2):
  A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3):
  A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Potentially life threatening (Grade 4)
  Emergency room visit or hospitalization.

The standardized grading scales for injection site assessment, vital signs assessment, clinical laboratory assessment, systemic (general), and systemic (illness) are provided in Section 10.5.

Assessment of Relatedness to Study Intervention

As VIS954 is a new investigational drug being investigated in healthy volunteers, AEs and SAEs should be considered related to study intervention unless there is another obvious etiology for the event (eg, motor vehicle accident or clear alternative etiologies).

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

Assessment of causal relationship of an AE to the study intervention is defined as follows:

- Related: There is a reasonable possibility of a temporal and causal relationship between study intervention and the AE.
- Not Related: There is no temporal or causal relationship between study intervention and the AE.

The investigator will use clinical judgment to determine the relationship.

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

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to IQVIA. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to IQVIA.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by IQVIA to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may

include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide IQVIA with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to IQVIA within 24 hours of receipt of the information.

10.3.5 Reporting of SAEs

SAE Reporting to IQVIA via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to IQVIA will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to IQVIA by telephone.

The contact for SAE reporting is provided in Section 10.3.7.

SAE Reporting to IQVIA via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to IQVIA.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

The contact for SAE reporting is provided in Section 10.3.7.

10.3.6 Reporting of Immediately Reportable Events

The primary mechanism for reporting an IRE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper IRE data collection tool (see next section for contact details) to report the event within 24 hours.

The site will enter the IRE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new IRE from a study participant or receives updated data on a previously reported IRE after the electronic data collection tool has been taken offline, then the site can report this information on a paper IRE form (see next section for contact details) or to the medical monitor by telephone.

The contact for IRE reporting is provided in Section 10.3.7.

10.3.7 Contact for Immediately Reportable Event Reporting

IQVIA

E-mail: CCI [redacted]

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential

Women in the following categories are considered participants of childbearing potential (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 1 year without an alternative medical cause.
  - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (> 40 IU/L or mIU/mL) is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Surgical sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2 Contraception Guidance

Contraception (described below) is required from the period prior to study enrollment, during the study, and until 30 days after the systemic exposure to the study intervention has ended for female participants (ie, 30 days after Day 56) and until 90 days after the systemic exposure to the study intervention has ended for male participants (ie, 90 days after Day 56).

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen-only hormone contraception associated with inhibition of ovulation[3] • Oral • Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) Male condoms must be used in addition to hormonal contraception.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception for this study. Additionally, the following methods are not considered highly effective:

- Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

While these are allowed in the study, they are not acceptable as sole methods of contraception for this study.

Note: Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Adverse Event Intensity Assessment

The standardized grading scales based on the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials, Sep 2007[12] are presented below.

Injection Site Assessment

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Pain	Does not interfere to activity	Repeated use of non- narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness[a]	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

[a]In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b]Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs Assessment

Vital Signs[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C)[b] (°F)[b]	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	Emergency room visit or hospitalization for arrhythmia
Bradycardia - beats per minute[c]	50 – 54	45 – 49	< 45	Emergency room visit or hospitalization for arrhythmia
Hypertension (systolic) - mmHg	141 – 150	151 – 155	> 155	Emergency room visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mmHg	91 – 95	96 – 100	> 100	Emergency room visit or hospitalization for malignant hypertension
Hypotension (systolic) – mmHg	85 – 89	80 – 84	< 80	Emergency room visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

[a]Subject should be at rest for all vital sign measurements.

[b]Oral temperature; no recent hot or cold beverages or smoking.

[c]When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Clinical Laboratory Assessment

The clinical laboratory values provided in the table below serve as a guideline and are dependent upon institutional normal parameters.

Serum[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**[b]
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
Creatine phosphokinase – mg/dL	1.25 – 1.5 x ULN[c]	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

Serum[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[b]
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

[a]The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[b]The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

[c]"ULN" is the upper limit of the normal range.

Hematology[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10800 – 15000	15001 – 20000	20001 – 25000	> 25000
WBC Decrease - cell/mm^3	2500 – 3500	1500 – 2499	1000 – 1499	< 1000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1500 – 2000	1000 – 1499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hyper eosinophilic

Hematology[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Platelets Decreased - cell/mm^3	125000 – 140000	100000 – 124000	25000 – 99000	< 25000
PT – increase by factor (prothrombin time)	1.0 – 1.10 × ULN[b]	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation

[a]The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

[b]"ULN" is the upper limit of the normal range.

Urine[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells transfusion

[a]The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Systemic (General)

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization

Systemic (Illness)

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Emergency room visit or hospitalization

11 References

1 Klos A, Tenner AJ, Johswich KO, Ager RR, Reis ES, Köhl J. The role of the anaphylatoxins in health and disease. Mol Immunol. 2009;46(14):2753-2766.

2 Klos A, Wende E, Wareham KJ, Monk PN. International Union of Basic and Clinical Pharmacology. LXXXVII. Complement Peptide C5a, C4a, and C3a Receptors. Pharmacol. Rev. 2013;65(1):500–543.

3 Monk PN, Scola AM, Madala P, Fairlie DP. Function, structure and therapeutic potential of complement C5a receptors: C5a receptors. Br J Pharmacol. 2007:152(4), 429–448.

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[redacted]

7 Harris CL. Expanding horizons in complement drug discovery: challenges and emerging strategies. Semin Immunopathol. 2018;40(1):125-140.

8 Dalakas MC, Alexopoulos H, Spaeth PJ. Complement in neurological disorders and emerging complement- targeted therapeutics. Nat Rev Neurol. 2020; 16(11):601-617.

9 Wagner F, Lange CF, Nowak M, Ignatenko S. FRI0315 First Human Dose of the Anti-C5a Receptor-Targeting, Human Monoclonal Antibody NNC0215-0384 in Patients with Rheumatoid Arthritis: A Phase 1, Randomised, Double-Blind, Single-Dose, Dose-Escalation Trial. Annals of the Rheumatic Diseases. 2014;73:499.

10 Carvelli J, Meziani F, Dellamonica J, Cordier P, Allardet-Servent J, Fraisse M, et al. Avdoralimab (Anti-C5aR1 mAb) versus placebo in patients with severe COVID-19: results from a randomized controlled trial (FOR COVID Elimination [FORCE]). Crit Care Med. 2022;50(12):1788-1798.

11 United States Food and Drug Administration. FDA authorizes Gohibic (vilobelimab) injection for the treatment of COVID-19. https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-gohibic-vilobelimab-injection-treatment-covid-19 Published on 04 Apr 2023. Acccessed on 19 Apr 2023.

12 United States Food and Drug Administration. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical Published in Sep 2007. Accessed on 20 Oct 2023.

Otsuka

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