STATISTICAL ANALYSIS PLAN

Protocol Number: 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.

AUTHOR: PPD

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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1.0	22AUG2024	PPD	Not Applicable – First Version

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of safety, pharmacokinetics, and pharmacodynamic data for Protocol VIS954-101. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 1.0, dated 07Sep2023 and amendment 1 dated 20Oct2023.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective 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

ECG = electrocardiogram; TEAEs = treatment-emergent adverse events.

2.2. Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary: • To assess the PK profile of	Secondary: *Pharmacokinetics* • The following PK parameters for VIS954 will be determined, as

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Objectives	Endpoints
VIS954	appropriate: • C_{max} • t_{max} • AUC_{0-inf} • AUC_{0-last} • $t_{1/2}$ • V_d/F • CL/F
• To determine the PD effect of VIS954	*Pharmacodynamics* • To characterize VIS954 C5aR1 RO (VIS954 binding)

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; RO = receptor occupancy; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of maximum serum concentration; V_d/F = apparent volume of distribution.

2.3. Exploratory Objectives and Endpoints

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3. STUDY DESIGN

3.1. General Description

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). Eligible 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 unblinded pharmacist. 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.

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 post-administration 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 A below. For more information, refer to Section 4.1 of the clinical study protocol.

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Table A: Planned dose of VIS954 for each cohort

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

3.2. Schedule of Events

Schedule of events can be found in Section 1.3 of the protocol.

3.3. Changes to Analysis from Protocol

The following changes to analysis from the protocol are included in this document:

- Section 9.2.7.1 of the protocol states that disposition data will be presented based on all participants randomized. But Section 5.3 of the protocol says minimal information for screen failure participants will be collected. Therefore, this document outlines the disposition table and the corresponding listing to be based on all participants who provided informed consent.
- CCI [redacted]

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4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Safety Monitoring Committee (SMC) meetings after at least 7 participants have completed ≥ 14 days in a cohort. IQVIA Biostatistics will not generate any listings or summaries for SMC meetings.
- Interim analysis 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.
- Blinded dry-run analysis prior to database lock in preparation of the final analysis.
- Final analysis post database lock.

4.1. Safety Monitoring Committee

Reporting for the SMC will be handled by the study clinic and operations team and is outside the scope of this document.

4.2. Interim Analysis

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 mentioned in Section 4.1, reporting for the SMC is outside the scope of this document. Additionally, 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.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of the SAP, identification of major protocol deviations requiring analysis exclusions, database lock, determination of analysis set exclusions, and unblinding of treatment.

Dry run analysis will be completed prior to the database lock, with the purpose of setting up all

programming deliverables using interim data transfers, in advance of the commencement of final analysis post database lock.

5. ANALYSIS SETS

Agreement and authorization of participants included/excluded from each analysis set will be conducted prior to the database lock and unblinding of the study.

5.1. Process for Analysis Set Assignment

The list of protocol deviations will be reviewed periodically during the study conduct and its impact on the inclusion of participants in the various analysis sets defined subsequently in this section will be assessed by the relevant members of the study team and documented.

5.2. Screened Analysis Set [SCR]

The screened analysis set (SCR) will contain all participants who provide informed consent for this study. Participants in this population will be used for disposition listings and summaries.

5.3. Randomized Analysis Set [RND]

The randomized analysis set will contain all participants who pass all eligibility criteria and are randomized to study treatment assignment.

5.4. Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all participants who receive study medication (active or placebo), and participants will be classified according to treatment received.

5.5. Pharmacokinetic Analysis Set [PKAS]

The pharmacokinetic analysis set (PKAS) will consist of all participants who receive active study drug

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(VIS954) and have at least 1 measured post-dose VIS954 serum concentration at a scheduled PK time after start of dosing for at least 1 PK analyte without protocol deviations or events with potential to affect the evaluation of the PK data. Participants in this population will be used for all PK analyses.

5.6. Pharmacodynamic Analysis Set [PDAS]

The pharmacodynamic analysis set (PDAS) will contain all participants who receive study medication (active or placebo) and have at least 1 measured PD value at a scheduled time point after start of dosing. Participants in this population will be used for all PD analyses.

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6. General Considerations

Derivation of the PK parameters for VIS954 in serum will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK, PD, CCI [redacted] and safety summaries, data listings and figures as well as the statistical analysis of the related variables will be the responsibility of the study biostatistician at IQVIA.

6.1. Summary Statistics

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative safety variables will be summarized using descriptive statistics, including the population size (N for sample size and n for available data), mean, standard deviation (SD), 95% confidence interval (CI), median, minimum, and maximum values. Descriptive statistics will be presented similarly for PK, PD, CCI [redacted] related quantitative variables with coefficient of variation expressed as a percentage (CV%) in place of

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95% CI. Geometric mean, and geometric CV% (GCV%) will be included for PK parameters, where applicable. Quartiles will be included for CCI [redacted] variables, where appropriate. CV% will not be presented for change from baseline results.

6.2. Treatment Summarization

In general, data will be presented and analyzed for each treatment group, for all VIS954 treated participants, and with placebo participants from all cohorts pooled into a single, overall placebo group. Data for Japanese and non-Japanese participants by treatment and overall, and all study participants will also be presented when appropriate. Participants will be analyzed according to the treatment they receive, instead of the planned (randomized) treatment.
For PK variables, the data will also be further summarized by Japanese and non-Japanese participants i.e., in addition to summarizing the PK variables by treatment group, the data will also be summarized stratified by non-Japanese participants and Japanese participants within each treatment group.

6.3. Precision

Safety variables i.e., clinical laboratory values, vital signs, electrocardiogram (ECG) intervals, and Wong-Baker FACES Pain Rating, including derivations thereof, such as change from baseline, will be reported to the same precision as the source data.

All PK concentrations, PD, CCI [redacted] results will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory [PK CCI [redacted] data from ICON lab and PD (receptor occupancy) from BioAgyltix] regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-participant listings. The rounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., t_{max}) will be reported with the

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same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the mean (arithmetic or geometric), SD, and CIs will be presented to one digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data. CV% will always be reported to 1 decimal place.

6.4. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears. Reference start date is defined as the day of study medication administration (Day 1 is the day of the study medication administration).

- If the date of the event is on or after the reference date, then:
- Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in APPENDIX 2.

6.5. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In absence of unscheduled assessments prior to dosing, the baseline will correspond to Day -1 assessment for physical examination, clinical safety laboratory, 12-lead ECG, PD, CCI [redacted] measurements; and will correspond to Day 1, Predose assessment for vital signs. In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline if the assessment is planned per protocol to take place prior to study medication administration. Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline unless otherwise indicated based on available start date/time combination or collected electronic Case Report Form (eCRF) data that identifies the

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individual event/medication as starting prior to study medication administration.

6.6. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit post-baseline summaries but will contribute to the best/ worst-case value where required (e.g., incidence tables for abnormal results by visit and treatment).
In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries.
Early termination data will be mapped to the end of study visit number for by-visit summaries.
Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.7. Statistical Tests

No formal statistical testing of hypotheses will be conducted. Exploratory statistical analyses may be carried out without drawing any inference, as documented in Section 3.3.

6.8. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Test Value at any post baseline Visit X – Value at Baseline assessment.

6.9. Software Version

All derivations, statistical analyses, summary tables, listings, and graphical figures will be generated using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.3 or higher (Certara, L.P. Princeton, New Jersey, United States of America [USA]).

7. STATISTICAL CONSIDERATIONS

7.1. Missing Data

Missing safety data will not be imputed.
Missing PK data will be handled as described in Section 15 of this analysis plan.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate emerging data collected during the actual study conduct.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study. Participant disposition will be tabulated for each treatment group and for all participants combined with the number of participants who are screened, randomly assigned to treatment, dosed, complete the study, prematurely discontinue, with the reason for early discontinuation. The number of participants in each of the analysis sets will also be included in the disposition table. A listing will present dates of completion or early withdrawal and the reason for early discontinuation, if applicable, for each participant.

Listings of inclusion/exclusion criteria failures, study eligibility, subject reconsent and rescreening, treatment assigned based on randomization with date and time of study treatment administration will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Individual participant demographics and baseline characteristics (medical history and results from drug and alcohol screens, serology screening, and pregnancy tests) will be presented in listings. Demographic characteristics such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) will be summarized and tabulated by treatment, for all active-treated participants, for Japanese and non Japanese participants, and for all participants overall for the safety analysis set. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex, race, ethnicity, and if the participant belongs to the Japanese or to the non-Japanese group. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. Derivations

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

11. PROTOCOL DEVIATIONS

11.1. Deviations Related to Study Conduct

A deviation from a protocol occurs when Investigator site staff or a study participant does not adhere to the protocol's stipulated requirements, whether inadvertently or planned. Protocol deviations will be listed and will include a classification of minor or major, as determined by clinical and medical staff. Protocol deviations will be reviewed by the study pharmacokineticist and biostatistician prior to unblinding to identify deviations which have the potential to affect the PK, PD, CCI [redacted] results.

11.2. Deviations Related to PK, PD CCI [redacted]

Changes to the procedures or events, which may impact the quality of the PK, PD, CCI [redacted] data, will be considered important protocol deviations, and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK, PD CCI [redacted]

Examples include, but may not be limited to:

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- Deviation from inclusion and/or exclusion criteria with potential to affect PK, PD[redacted]
- Deviation from study restrictions with potential to affect PK, PD[redacted]
- Concomitant medications that can affect PK, PD[redacted]
- Missed, incomplete, or incorrect dosing.
- Sample handling/processing errors.
- Bioanalytical issues affecting the data.
- Missing concentrations/not collected samples at key times in PK profile.
- Significant time deviations at key times in PK profile.
- Other protocol deviations with potential to affect PK, PD[redacted]

In the case of an important protocol deviation or event, PK, PD[redacted] data collected during the affected treatment period will be excluded from the study results. Excluded data and the reason(s) for exclusion will be described in a listing. A summary of important protocol deviations will be tabulated by treatment group. Other changes to the procedures or events which do not impact the quality of the PK and PD data will not be considered important protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times (that do not occur at key times in the profile).

12. MEDICAL HISTORY

Medical History information will be presented for the SAF. Medical History conditions are defined as those conditions which stop prior to study drug administration. Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary version 26.1.

- Presented by System Organ Class (SOC) and Preferred Term (PT) and all participants combined.
- The number and percentage of participants with at least one condition in each SOC and each PT will be summarized by treatment group.
- By treatment, each participant's medical history will be listed with SOC and PT.

13. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be presented for the SAF. All medications will be coded using World Health Organization's WHODrug Global B3 dictionary version Sep2023. Medications will be listed

[redacted]

and summarized by treatment and Anatomical Therapeutic Chemical (ATC) Level 3 classification.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the study medication administration.
- 'Concomitant' medications are medications which:
    - started prior to, on or after the study medication administration and started no later than 71 days following end of study medication,
    - AND ended on or after the study medication administration or were ongoing at the end of the study.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication will be presented for the SAF. A listing with participants presented by treatment group, including the dosing dates and times, dose levels and dosing errors, if any, will be provided. A summary of exposure will be presented including the number of participants receiving the full dose, partial dose, and not receiving any dose by treatment, for all VIS954 treated participants, and for all participants combined.

15. PHARMACOKINETIC ANALYSIS

Pharmacokinetic concentration and parameter listings will include data for all treated participants. Descriptive statistic summaries and figures for PK analysis (serum) will be based on the PKAS . Summary statistics for PK concentrations and parameters will be presented for all participants in each dose level and by Japanese versus non-Japanese; Additionally, summary statistics for PK concentrations will be presented for all participants in each dose level and by ADA status (positive and negative). The summary statistics will include N, n, mean, SD, median, minimum, maximum, CV%. Geometric mean and geometric CV% will be presented for PK parameters, except for t_{max} for which only N, n, median, minimum, and maximum will be reported.

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15.1. Serum Concentration Data

Participants with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

Whole blood samples will be collected for measurement of serum concentrations of VIS954 at the time points specified in protocol Section 1.3. A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Samples that are outside the protocol-specified collection windows (calculated from the time zero point [e.g., time of drug administration] or the last relevant activity) will be identified, as well as participants that are excluded from the PKAS.

Serum concentrations will be summarized using descriptive statistics by Japanese versus non-Japanese, ADA status (positive and negative) and overall, for each treatment group. Results for samples which were collected outside the specified collection window will be included in the descriptive statistics and will be included in the calculation of PK parameters unless otherwise warranted by the data (i.e., in case of a protocol deviation impacting the validity of the sample collected such as a predose sample collected after dosing, or a postdose sample collected prior to dosing, etc.), but such results will be flagged in the listing. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics.

A by-treatment participant listing of all concentration-time data for each cohort will be presented. Figures of arithmetic mean concentration-time data (±SD, as appropriate) will be presented for each cohort, by Japanese versus non-Japanese and ADA status (positive and negative) within each treatment group on linear and semi-logarithmic scales. Individual participant concentration-time data will be graphically presented on linear and semi-logarithmic scales using different symbols for Japanese and non-Japanese participants. All concentrations of VIS954 which were found to be BLQ for the PK assay during analysis will be imputed to and plotted at the nominal value of the LLOQ (25 ng/mL, i.e. 0.025 ug/mL) for all graphs which use a semi-logarithmic scale axis.

15.2. Pharmacokinetic Parameters

For PK parameter calculations, predose samples that are BLQ or missing will be assigned a numerical

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value of zero. Any anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters. Pharmacokinetic parameters will be computed if the anomalous concentration is not greater than 5% of the observed maximum concentration (C_{max}). If the anomalous concentration is greater than 5% of C_{max}, the PK parameters for the given participant will be calculated and reported in the listing but excluded from statistical summaries and analyses.

Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following C_{max}, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to zero. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

The following PK parameters will be estimated for VIS954 in serum by non-compartmental methods using actual elapsed time from dosing. A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters:

C_{max}	Maximum serum concentration (µg/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time of maximum serum concentration (hr), obtained directly from the observed concentration versus time data.
$AUC_{0\text{-last}}$	Area under the concentration-time curve in serum from predose to time of last quantifiable concentration (hr*µg/mL), calculated by linear up/log down trapezoidal summation.
$AUC_{0\text{-inf}}$	Area under the concentration-time curve in serum from predose extrapolated

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	to infinite time (hr*µg/mL), calculated by linear up/log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{0\text{-last}} + C_{last}/\lambda_z$.
$t_{1/2}$	Apparent terminal half-life (hr), determined as $\ln 2/\lambda_z$.
CL/F	Apparent clearance after extravascular dosing (L/hr), calculated as dose divided by $AUC_{0\text{-inf}}$.
V_d/F	Apparent volume of distribution following extravascular dosing (L), calculated as dose divided by $[\lambda_z \cdot AUC_{0\text{-inf}}]$
DNC_{max}	Dose normalized C_{max} (µg/mL/mg)
$DNAUC_{0\text{-last}}$	Dose normalized $AUC_{0\text{-last}}$ (hr*µg/mL/mg)
$DNAUC_{0\text{-inf}}$	Dose normalized $AUC_{0\text{-inf}}$ (hr*µg/mL/mg)

The following PK parameters will be calculated for diagnostic purposes and listed but will not be summarized.

$t_{1/2}$, Interval	The time interval (hr) of the log-linear regression to determine λ_z.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z. A minimum of 3 data points will be used for determination.
λ_z	Apparent terminal rate constant (1/hr), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of 3 data points will be used for determination.
Adjusted Rsq	Goodness of fit statistic for calculation of λ_z (Regression coefficient). If the Adjusted Rsq value is less than 0.800 then $AUC_{0\text{-inf}}$ and $t_{1/2}$ will be listed but not summarized.

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$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC_{0\text{-}inf}\times 100]$. If the $\%AUC_{ex}$ is greater than 20% of $AUC_{0\text{-}inf}$, then $AUC_{0\text{-}inf}$ will be listed but not included in summary and inferential statistics. Associated parameters (CL/F and V_d/F) will be listed but not included in summary statistics as well.

Pharmacokinetic parameters will be summarized by each cohort and by Japanese versus non-Japanese within each active treatment group using descriptive statistics and listed by participant (as applicable). Geometric mean, and geometric CV% will not be calculated for t_{max}. Scatter plots of individual and geometric mean of PK parameters, C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ versus dose will be presented.

15.3. Pharmacokinetic Statistical Analysis

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16. PHARMACODYNAMIC ANALYSIS

16.1. Pharmacodynamic Measurements

The PD analysis will be based on the PDAS. A listing of PD blood sample collection dates and times will be provided for PD testing of Complement 5a receptor 1 (C5aR1) Receptor Occupancy (RO; VIS954 binding). For all PD endpoints, participant listings of all observed data over time will be presented by treatment.

%RO Neutrophils CCI [redacted] are the primary PD endpoints of interest and will be summarized using descriptive statistics by treatment group. Figures of mean %RO over time data will be presented with error bars (defined as mean ± SD) by treatment group. Similarly, figures of median %RO over time data will be presented by treatment group. Individual observed %RO over time data for each participant will be graphically presented separately for each treatment group. Baseline data will be taken as the last measurement prior to dosing.

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- Time spent above 40% RO, defined as duration in hours from date and time of dosing until the date and time of PD collection when %RO > 40%
- CCI [redacted]

Each derived PD variable above will be listed by participant and summarized with descriptive statisics by treatement group. CCI [redacted]

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16.2. Pharmacodynamic Parameters

Not applicable to this study.

16.3. Pharmacokinetic-Pharmacodynamic Relationships

Not applicable to this study.

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18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. Adverse Events

Definitions of AE, unsolicited AE, and solicited AE can be found in Section 10.3 of the clinical study protocol. Unsolicited Adverse Events (AEs) will be coded using MedDRA central coding dictionary, version 26.1.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occur or worsen in severity after the study medication administration, and up to Day 71 (including the follow-up period) after the study medication administration.

Pretreatment AEs are defined as AEs occurring prior to dosing. These events will be presented in the listings only and will not be included in the tabular summary of AEs.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e., treatment emergent.

Solicited AEs are predefined local injection site reactions and systemic events for which the participant is specifically questioned, and responses recorded in the eCRF data. These are collected at predefined timepoints of 1 and 4 hours post dose (Day 1), 24 hours post dose (Day 2), and on Days 3 and 29 for tenderness, pain, erythema/redness, and induration/swelling with responses based on the severity of each condition as Mild, Moderate, Severe, or Potentially Life-threatening.

18.1.1. All TEAEs

Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and relationship to study medication.

18.1.1.1. SEVERITY

Severity is classed as mild/ moderate/ severe/ potentially life threatening (increasing severity) as judged by

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the investigator per protocol requirements. TEAEs starting after the study medication administration with a missing severity will be classified as severe. If a participant reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

18.1.1.2. RELATIONSHIP TO STUDY MEDICATION

Relationship, as indicated by the Investigator per protocol requirements, is classed as "related" or "not related". A "related" TEAE is defined as a TEAE with a relationship to study medication assessed as "related" by the Investigator based on if there is a reasonable possibility of a temporal and causal relationship between study intervention and the AE. TEAEs with a missing relationship to study medication will be regarded as "related" to study medication. If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship ("related") to study medication will be used in the corresponding relationship summaries.

All AE tabulations will be performed by dose level, for all active-treated participants, and overall participants; and will include the number and percentage of participants. AEs for participants treated with placebo from all cohorts will be pooled together in a single placebo group. Incidence of unsolicited TEAEs will be tabulated by the following:

- Across all SOC and PT, By Severity, by Relationship, by Leading to Study Discontinuation, and by Seriousness.
- By SOC and PT.
- By SOC, PT and Maximum Severity.
- By SOC, PT for AEs Related to study medication only.
- By SOC, PT and Maximum Severity for AEs Related to study medication.
- By SOC, PT and participants' Overall ADA Status.

18.1.2. Injection Site Reactions (Solicited Adverse Events)

Solicited AEs are a list of pre-defined events or symptoms that participants are assessed for at designated time points post dose. Injection site assessment will be performed by the investigator or designee at 1 hour, 4 hours, 24 hours post dose, and on Day 3, and Day 29 based on the following reactions:

- Tenderness

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- Pain
- Erythema/Redness
- Induration/Swelling
- Other reactions as observed by the investigator.

Each of these reactions, if observed, will be graded for severity on a 4-point categorical scale of Mild, Moderate, Severe, and Potentially Life-threatening, as per protocol. Solicited AEs will be tabulated for incidence of occurrence for number of participants by timepoint and treatment group. The summaries will be presented by the specific local injection site reaction and the severity of the assessment of the condition as recorded on the eCRF data. The summaries will also be presented by severity and overall for all timepoints, overall for all VIS954 treatment groups, and for all participants. The number of participants experiencing any injection site reactions will be plotted by treatment group and severity in a stacked bar graph.

18.1.3. TEAEs Leading to Withdrawal from the Study

TEAEs leading to withdrawal from the study will be identified in the AE listing by using the recorded response to the relevant question in the eCRF page.

18.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF and will be listed separately in addition to being included in other AE listings.

18.1.5. Immediately Reportable Events

Immediately Reportable Events (IREs) are those events recorded as "Immediately Reportable Event" on the Adverse Events page of the eCRF and will be listed separately in addition to being included in other AE listings.

18.1.6. Deaths

If any participants die during the study as recorded in seriousness criteria of the SAE page of the eCRF,

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the information will be presented in a separate data listing in addition to being included in other AE listing.

18.2. Laboratory Evaluations

Results from the local laboratory will be included in the reporting of this study for clinical laboratory analytes in the Hematology, Serum Chemistry and Coagulation, and Urinalysis panels. A list of laboratory assessments to be included in the outputs is included in Appendix 2 of the clinical study protocol, Section 10.2. Presentations will use SI Units.
Quantitative laboratory measurements reported as "< X", i.e., BLQ, or "> X", i.e., above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Observed and change from baseline by treatment group and visit (for quantitative measurements).
- For participants with both baseline results as well as for the postbaseline visit, shift from baseline according to normal range criteria by treatment group and visit (for quantitative measurements and categorical measurements)

18.2.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

18.2.2. Toxicity Grading for Laboratory Data

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 in clinical study protocol Section 10.5. Based on these criteria the clinically significant

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laboratory test abnormalities assessed as AEs by the principal investigator will be presented in the AE listings.

18.3. ECG Evaluations

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- QTcF Interval (msec) [derived]
- Hear Rate (HR) (beats per minute [bpm])
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Observed and change from baseline descriptive statistics by treatment group and visit (for quantitative measurements)
- Incidence of clinically significant Overall ECG assessments based on investigator's assessment by treatment group and visit.

18.4. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)

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- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (°C)
- Height (cms)
- Weight (kg)
- BMI (kg/m^2)

The following summaries will be provided for vital signs data:

- Observed and change from baseline descriptive statistics by treatment group, visit, and timepoint.
- Incidence of clinically significant vital signs assessment based on investigator's assessment by treatment group, visit, and timepoint.

18.5. Physical Examination

Physical exam results will be listed including specification of any abnormalities observed and the investigators assessment of the abnormality. A shift table summarizing the changes in physical examination assessments from baseline to post baseline visits will be provided.

18.6. 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 same time points when solicited AEs will be assessed. Data for the Wong-Baker FACES Pain Rating Scale scores for pain perception will be summarized using descriptive statistics.

19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

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20. REFERENCES

Smith BP, et al. Confidence Interval Assessment of Dose Proportionality. Pharm Res. 2000;17:10.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following:

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	For Tables and Listings	For Figures
Placebo (where applicable)	Placebo (where applicable)	Placebo (where applicable)
CCI VIS954	CCI VIS954	CCI
CCI VIS954	CCI VIS954	
CCI VIS954	CCI VIS954	
CCI VIS954	CCI VIS954	

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Treatment Group	For Tables and Listings	For Figures
Placebo (where applicable)	Placebo (where applicable)	Placebo (where applicable)
CCI [redacted] VIS954	CCI [redacted] VIS954	CCI [redacted]
[redacted] VIS954	[redacted] VIS954	[redacted]
All VIS954 Treated (where applicable)	VIS954 (where applicable)	VIS954 (where applicable)
All Subjects (where applicable)	All Subjects (where applicable)	All Subjects (where applicable)

Presentation of Visits

Include rows/columns as appropriate.

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening, Day -28	Scr (V1)
Baseline, Day -1	BL (V2)
Day 1	D1 (V3)
Day 2	D2 (V4)
…	
Day 57	D57 (V14)
EOS Day 71/ET	D71 (V15)

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Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment group
- Participant ID
- Date and time (where applicable).

APPENDIX 2. PARTIAL DATE CONVENTIONS

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post study
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'

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START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

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