STATISTICAL ANALYSIS PLAN

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in Participants with Immunoglobulin A (IgA) Nephropathy

Protocol VIS649-201

Protocol Number:	VIS649-201
Protocol Version and Date:	Version 4.0: 08 December 2020 Version 3.0: 27 January 2020 Version 2.0: 26 November 2019
Name of Test Drug:	VIS649
Phase:	Phase 2
Methodology:	Randomized, Double-Blind, Placebo-Controlled, Multiple Dose
Sponsor:	Visterra, Inc. 275 2nd Avenue Waltham, MA 02451 Tel: (617) 498-1070
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Analysis Plan Date:	27 Jun 2023
Analysis Plan Version:	Version 5.0

APPROVAL SIGNATURE PAGE

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in Participants with Immunoglobulin A (IgA) Nephropathy
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Veristat™, LLC. Author:

[redacted]

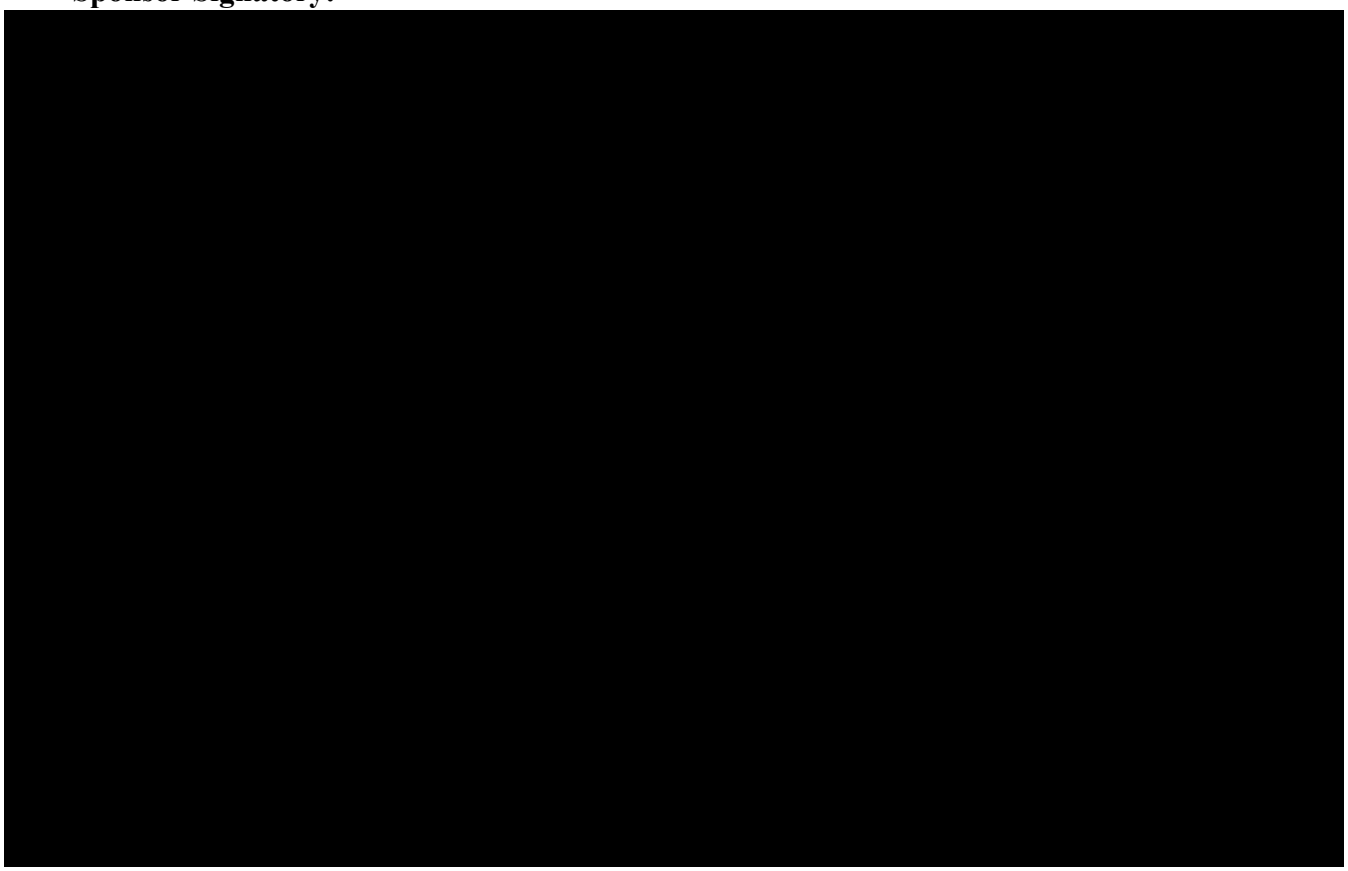
Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:



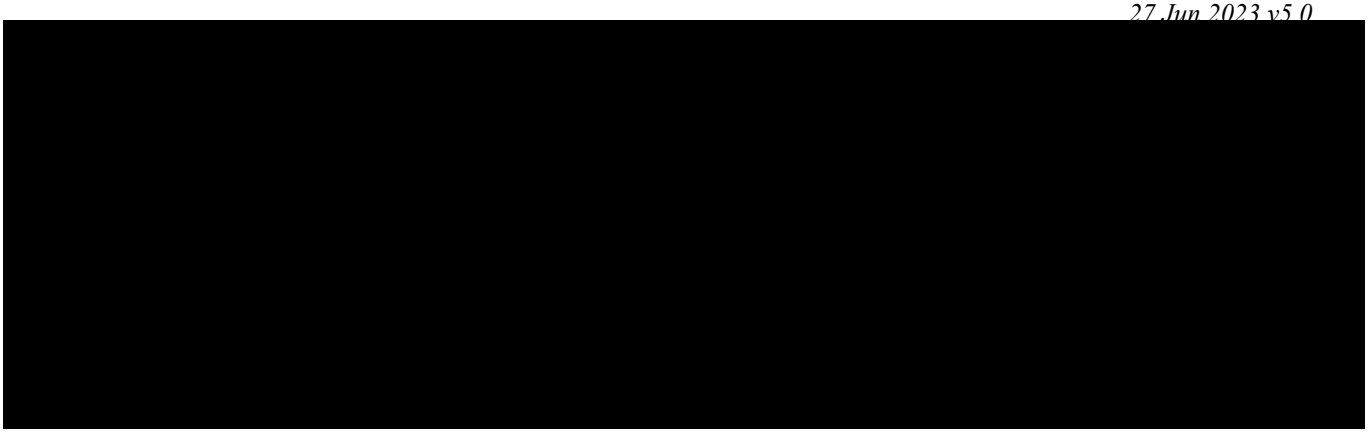


TABLE OF CONTENTS

TABLES INCLUDED IN THE TEXT

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACEi	Angiotensin-converting enzyme indicator
ADA	Antidrug antibody
AE	Adverse event
ANCOVA	Analysis of covariance
APRIL	A Proliferation Inducing Ligand
ARB	angiotensin receptor blocker
AUC_{∞}	Area under the plasma drug concentration – time curve from time 0 to infinite time
$AUC_{0\text{-}30day}$	Area under the plasma drug concentration – time curve from time 0 to 30 days post dose
AUC_{τ}	Area under the plasma drug concentration – time curve from time 0 to the end of the dosing period
BAFF	B cell activating factor
BCMA	B-cell maturation antigen
BMI	Body Mass Index
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
Gd-IgA1	Galactose deficient immunoglobulin A_1
HR	Heart Rate
Ig	Immunoglobulin
IgA	Immunoglobulin A

Abbreviation	Definition
IgAN	Immunoglobulin A nephropathy
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicine product
ITT	Intent-to-treat
IV	Intravenous
LLOQ	Lower limit of quantification
LSM	Least-square mean
LSMD	Least-square mean difference
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MMRM	Mixed Model with Repeated Measurements
MNC	Mononuclear cell
OR	Odds ratio
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
ROW	Rest of World
SAP	Statistical analysis plan
SBP	Systolic Blood Pressure
SD	Standard deviation
SE	Standard Error
SIA	Systemic immunosuppressive agent
SOC	Standard of care
TACI	Transmembrane activator and calcium-modulator cyclophilin ligand interactor

Abbreviation	Definition
TBNK	Hematology/flow panel where T = T cells, B = B cells and NK = NK cells.
TEAE	Treatment-emergent adverse event
TNC	Total nucleated cell count
uACR	Urinary albumin/creatinine ratio
uPCR	Urine protein to creatinine ratio
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

VIS649 is a humanized immunoglobulin G2 monoclonal antibody being developed for the treatment of immunoglobulin A nephropathy (IgAN), an autoimmune glomerulonephritis characterized by the deposition of immunoglobulin A (IgA)-containing immune complexes in the kidney.

IgAN is one of the most common primary glomerular diseases and affects patients globally, with some geographical variation in incidence and prevalence (Wyatt and Julian 2013, Rodrigues, Haas et al. 2017, Schena and Nistor 2018). Clinical presentation varies from incidentally detected asymptomatic hematuria and proteinuria to rapidly progressive glomerulonephritis requiring dialysis. IgAN is a significant cause of chronic kidney disease and end-stage renal disease (ESRD), with 30–40% of patients reaching ESRD 20–30 years after the first clinical presentation. IgAN can occur in either sporadic (90–95%) or familial (5–10%) patterns. Patients with familial IgAN might have poorer prognoses than those with sporadic disease, with an increased risk of progression to renal failure (Lai, Tang et al. 2016).

The primary parameter of this study, proteinuria, is an important marker of progression of renal disease in patients with IgAN. Patients with significant proteinuria (> 1.0 g/day) have a faster decline of estimated glomerular filtration rate (eGFR) and progression to ESRD, when compared to patients with lower degrees of proteinuria (< 500 mg/day). Hence, reduction in proteinuria is a crucial aspect in the management of IgAN (Reich, Troyanov et al. 2007, Nam, Kie et al. 2014, Inker, Mondal et al. 2016). Proteinuria is also gaining acceptance by health authorities as a surrogate marker of eGFR decline in IgAN (Inker, Lesley et al. 2021).

The mechanistic target of VIS649 is the cytokine A Proliferation Inducing Ligand (APRIL). APRIL belongs to the tumor necrosis factor ligand superfamily and has emerged as a key factor in the pathogenesis of IgAN. APRIL mediates the immunoglobulin (Ig) isotype switch during B-cell development, production of IgA, and plasma-cell survival, and may specifically influence production of aberrantly Galactose deficient immunoglobulin A_1 (Gd-IgA1) (Castigli, Scott et al. 2004, Varfolomeev, Kischkel et al. 2004, Endo, Nishio et al. 2007, Bossen, Cachero et al. 2008). Studies in patients with IgAN have shown that elevated APRIL levels correlate with poor kidney outcomes when compared with patients with lower APRIL levels (Han, Yang et al. 2016, Zhai, Zhu et al. 2016). A similar trend is also seen with Gd-IgA1 levels, with higher levels associated with faster and more frequent progression to kidney failure when compared to patients with lower Gd-IgA1 levels (Castigli, Scott et al. 2004, Berthoux, Suzuki et al. 2012, Zhao, Hou et al. 2012).

VIS649 binds to and blocks the biological actions of APRIL, preventing its binding to its receptors, transmembrane activator and calcium-modulator cyclophilin ligand interactor (TACI), and B-cell maturation antigen (BCMA). Blocking the biological actions of APRIL

reduces the production of IgA. The hypothesis to be tested in this study is that blocking the biological actions of APRIL in patients with IgAN will lead to reduction of serum IgA (including Gd-IgA1) levels and will reduce or halt the progression of IgAN, as measured by decrease in proteinuria and stabilization of eGFR decline.

1.1.2. Study Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data to assess the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the efficacy interim and final analysis outputs and the results and appendices of the clinical study report (CSR) for this trial.

This SAP will also outline any changes in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.2.1. Primary Safety Objective

To evaluate the safety and tolerability of monthly doses of VIS649 at each of 3 dosing levels, administered intravenously (IV) to IgAN participants over the course of 12 months as an add-on to standard of care (SOC) treatment with angiotensin-converting enzyme indicator/angiotensin receptor blocker (ACEi/ARB) therapy compared with saline placebo infusions.

1.1.2.2. Primary Efficacy Objective

To evaluate the dose response of monthly doses of VIS649 on proteinuria at each of 3 dosing levels, administered IV to IgAN participants over the course of 12 months as an add-on to SOC treatment with ACEi/ARB therapy compared with saline placebo infusions.

1.1.2.3. Secondary Objectives

- To evaluate the effect of repeated doses of VIS649 at 3 dosing levels versus placebo on the following parameters:
    - Urine protein to creatinine ratio (uPCR) at Months 9 and 16 (ie, 5 months following the final [12^{th}] monthly dose administration)
    - 24-hour urine protein excretion at Months 9, 12, and 16
    - Number of participants in each group achieving a ≥ 30% decline from baseline in uPCR at Months 9, 12, and 16
    - Clinical remission, defined as reduction in 24-hour urine protein excretion to < 300 mg/day for at least 3 consecutive months

- eGFR at Months 12 and 16
- Pharmacodynamic (PD) parameters, inclduing IgA, Immunoglobulin G (IgG), and Immunoglobulin M (IgM) concentrations

- To determine the pharmacokinetic (PK) profile of repeated dose of VIS649 at each dosing level
- To determine the PK/PD profile of VIS649, relating VIS649 PK parameters and biomarkers such as changes in IgA to changes in proteinuria and eGFR
- To screen for anti-VIS649 antibodies (ADA) responses

1.1.2.4. Exploratory Objectives

[redacted]

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety and efficacy of IV administered VIS649 over a 12-month treatment course in participants with IgAN.

Participants will be enrolled from approximately 100 global sites in approximately 16 countries. Enrolled participants will be 18 years of age or older with an IgAN diagnosis confirmed by biopsy.

VIS649 (2, 4, and 8 mg/kg) or placebo will be administered as 12 monthly IV infusions (Months 0-11) as described in the schedule of assessments (Current Version of Protocol). The final efficacy assessments will be taken at the Month 12 Visit (ie, around Day 360, following approximately 12 months of exposure to study drug), and a final safety evaluation will be conducted at Month 16 (ie, approximately 5 months following last study drug dosing). Up to 60 participants (approximately 15 participants in each treatment group) may have a more intensive PK and PD sampling schedule at Months 0-3 and 11-14 (see Current Version of Protocol).

Efficacy assessments will be primarily evaluated by the reduction in uPCR from baseline. The timepoints to be used for uPCR urine collections are referred to as either Schedule 'A' or 'B', depending on whether the uPCR are collected from the 24-hour urine collection (or an intended 24-hour urine sample) (i.e., '24-hour' Schedule A Urine Collection) or not (ie, 'Spot' Schedule B Urine Collection). Schedule A Urine Collection visits include Screening, Days 270 (Month 9), 360 (Month 12) and 485 (Month 16), where Screening would be the Baseline visit. Schedule B Urine Collection visits include Day 1 (pre-infusion) and Days 8, 30, 60, 90, 120, 150, 180, 210, 240, 300 and 330, where Day 1 (pre-infusion) would be the Baseline visit.

Safety assessments will include review of adverse events (AEs) (including hypersensitivity reaction, anaphylactic reaction, and injection site tolerability), physical examinations, clinical laboratory assessments (including biochemistry, hematology, urinalysis, and pregnancy testing), laboratory testing (including serum Ig levels and ADAs), vital sign measurements, and use of concomitant medications.

The total study duration for each participant (from screening to end-of-study) will be up to 17 months (assuming up to 1 month for screening, 12 months for monthly doses [including 30 days after the 12th dose]), and follow-up visits up to 155 days after the last dose of study intervention.

1.2.2. Randomization Methodology

Participants will be randomly assigned in a 1:1:1:1 allocation ratio to receive VIS649 at 2, 4, or 8 mg/kg or placebo, with approximately 36 participants randomized to each treatment group.

Randomization will be stratified by region (Japan vs Rest of World [ROW]). A target of 12 or more participants are planned to be randomized at Japanese sites. Japanese participants will be randomized with equal allocation and without further stratification. Randomization for ROW will be stratified by screening uPCR (Schedule A, ≤ 2.0 g/g vs > 2.0 g/g). Further details about the creation of randomization schemes, and other randomization procedures, can be found in the Randomization Plan (Appendix 1).

1.2.3. Discontinuation of Study Treatment and Withdrawal from Study

Participants have the right to discontinue study treatment or withdraw from the study at any time for any reason. Participants may withdraw or be withdrawn from study-related procedures and interventions for the following reasons:

- Adverse Event
- Death
- Lost-to-Follow-up
- Protocol Violation
- Physician Decision
- Study Terminated by Sponsor
- Withdrawal by Subject
- Other

Reasons of study discontinuation will be listed and summarized in the CSR.

At the discretion of the Data Safety Monitoring Board (DSMB), in consultation with the study Sponsor, the participant may be discontinued from treatment or study. Furthermore, the DSMB may recommend the trial to be modified or cease for safety reason(s). More specific information can be found in the DSMB Charter.

1.2.4. Study Procedures

The schedule of assessments is presented in the latest version of the study protocol.

1.2.5. Study Endpoints

1.2.5.1. Primary Efficacy Endpoint

The primary efficacy endpoint is measured by the change from baseline in uPCR (measured on the natural log scale from 24-hour urine collection or the intended 24-hour urine collection) at Month 12 (ie, approximately 30 days after the 12^{th} dose is administered).

1.2.5.2. Secondary Endpoints

Secondary endpoints include:

- Change from baseline in uPCR on natural log scale (from 24-hour urine collection or the intended 24-hour urine collection) at Months 9 and 16
- Change in 24-hour urine protein excretion (mg/day) from baseline to Months 9, 12, and 16
- Number of participants in each group achieving a ≥ 30% decline from baseline in uPCR (from 24-hour urine collection or the intended 24-hour urine collection) at Months 9, 12, and 16
- Number of participants in each group achieving reduction in 24-hour urine protein excretion to < 300 mg/day at Months 9, 12, and 16, as well as the proportion of participants who have achieved reduction in 24-hour urine protein excretion to < 300 mg/day at (1) Month 9 and maintained the response through Month 12 and (2) at Month 12 and maintained the response through Month 16
- Linear slope eGFR (mL/min/1.73 m^2) between baseline and Month 12
- Linear slope eGFR (mL/min/1.73 m^2) between baseline and Month 16
- Change in eGFR (mL/min/1.73 m^2) between baseline and Months 12 and 16
- Percent change from baseline in total serum IgA, IgG, and IgM concentrations at Months 9, 12, and 16 (mg/dL)
- Serum PK Parameters (See Section 1.2.5.4)
- Serum ADA levels (See Section 1.2.5.5)

1.2.5.3. Exploratory Endpoints

Exploratory endpoints include:

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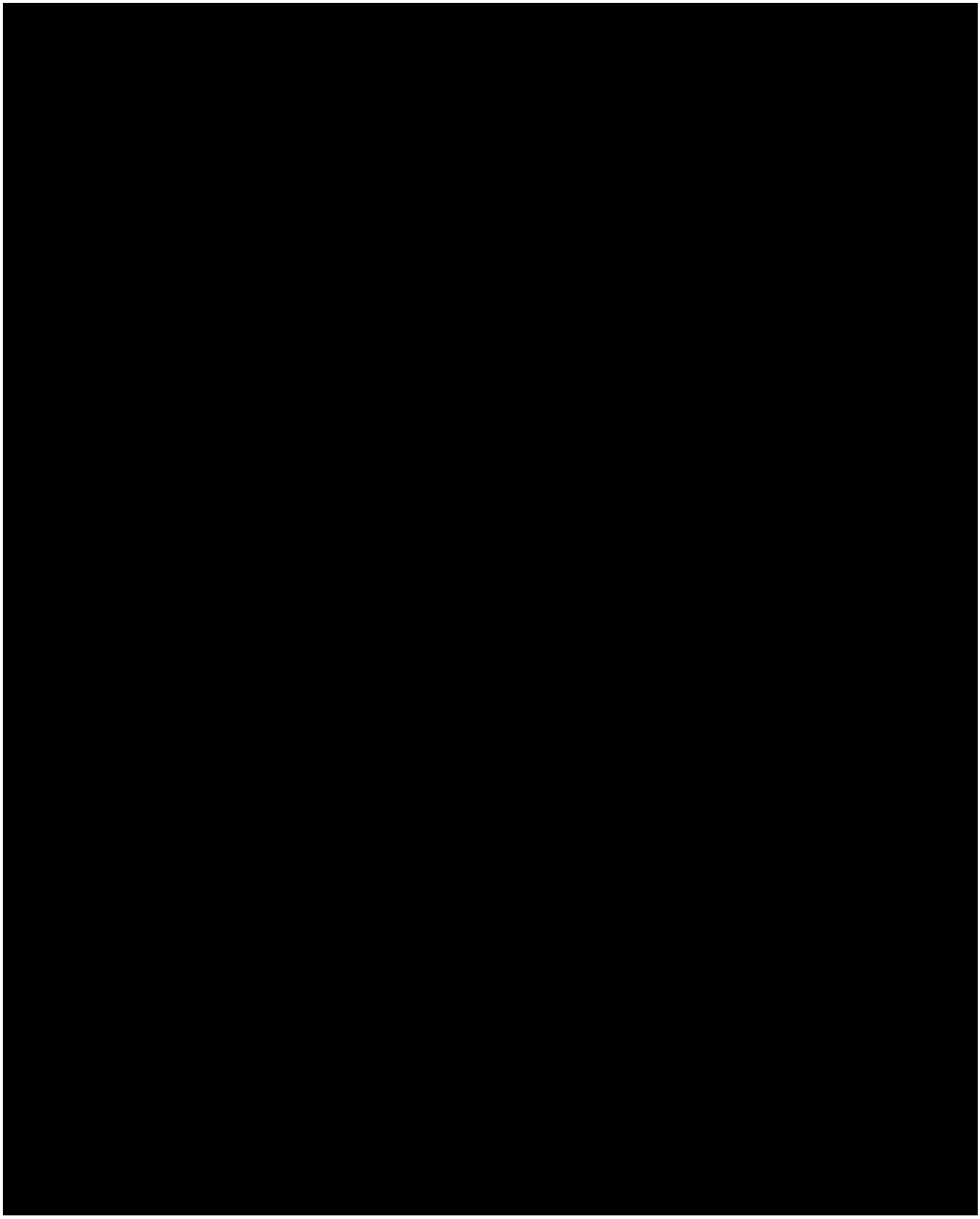

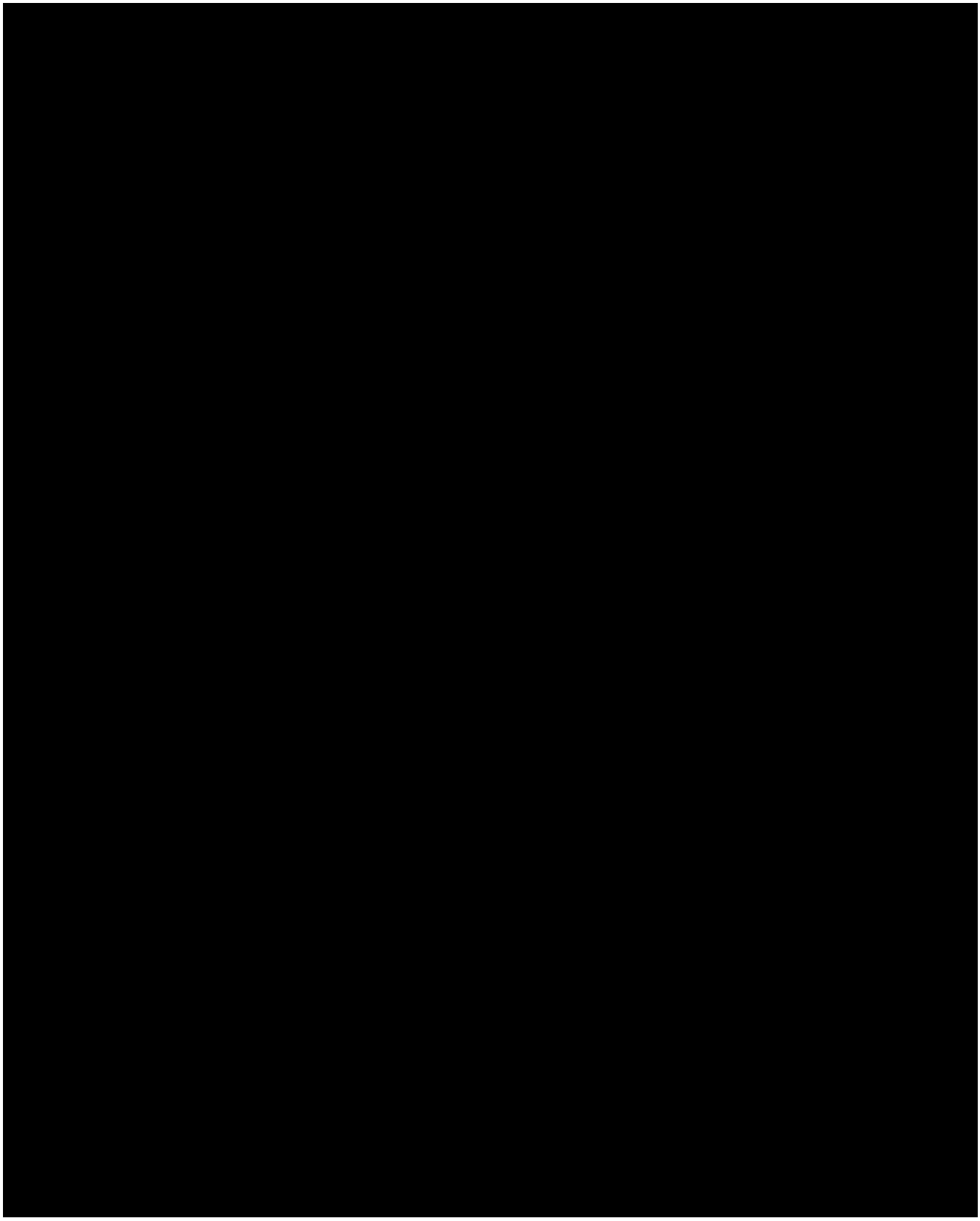

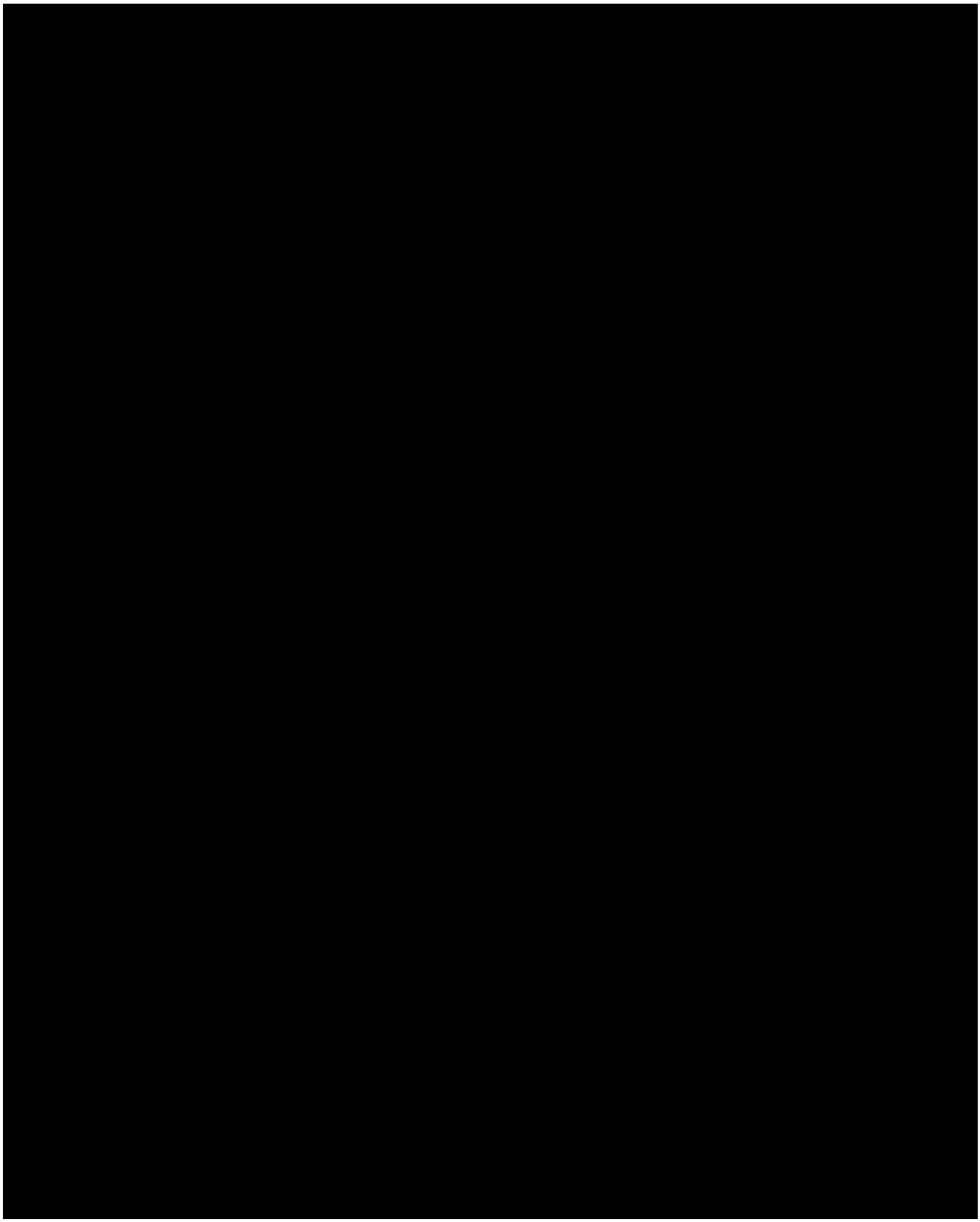

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1.2.5.4. Pharmacokinetic Endpoints

Circulating serum concentrations of VIS649 will be reported pre- and post-VIS649 infusion (see Current Version of Protocol for sample collection schedule). Additionally, the VIS649 PK parameters described in Table 4 will be calculated from participants in the intensive PK Population where additional blood samples will be collected at Months 0 and 11 (see Current Version of Protocol for PK Population sampling schedule). At Month 11, it is expected that there will be drug accumulation and possibly steady state; therefore, the PK parameters calculated will vary between Months 0 and 11 as shown in Table 4.

Table 4 Pharmacokinetic Parameters

Pharmacokinetic Parameter	**Unit**	**Description**	**Month(s)**
C_{max}	µg/L	Maximum observed plasma concentration	0 & 11
T_{max}	day	Time at which the maximum plasma concentration occurs	0 & 11
AUC_{∞}	day*µg/L	Area under the concentration-time curve from time zero extrapolated to infinity	0
$AUC_{0\text{-}30day}$ (dosing interval)	day*µg/L	Area under the time concentration curve from time 0 (relative to dose) to Day 30	0 & 11

Pharmacokinetic Parameter	**Unit**	**Description**	**Month(s)**
AUC_{τ}	day*µg/L	Area under the time concentration curve from time 0 (relative to dose) the end of the dosing period	11
$t_{1/2,z}$	day	Terminal elimination half-life calculated as: 0.693/lambda z	0 & 11
Vss	L	An estimate of the volume of distribution at steady state	0 &11
CL	L/day	Clearance calculated as: Dose/AUC ∞	0
CL_{ss}	L/day	Clearance at steady state calculated as: Dose/AUC_{τ}	11
$R_{ac}(AUC_{0\text{-}30day})$	ratio	Accumulation ratio calculated as: $AUC_{0\text{-}30day}$ at Month 11 / $AUC_{0\text{-}30day}$ at Month 0	11

1.2.5.5. Immunogenicity Endpoints

Immunogenicity endpoints include serum anti-VIS649 ADA levels, the positive/negative results of a confirmatory ADA assay, antibody titer, and neutralizing antibody results, as applicable.

1.2.5.6. Safety Endpoints

Safety evaluations performed during the study include physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations including

hematology, serum chemistry, urinalysis, pregnancy, serum Ig levels, ADAs, monitoring of AEs and concomitant medications.

2. PARTICIPANT POPULATION

2.1. Population Definitions

The following participant populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: All participants who are randomized. Participants will be categorized by treatment they were randomized to receive.

- Modified Intent-to-Treat (mITT) Population: All randomized participants who received at least 1 dose of study treatment. Participants will be categorized by treatment that they were randomized to receive. The mITT population will be the primary population for assessment of efficacy.

- Safety Population: All randomized participants who received any amount of study treatment. Participants will be categorized by treatment received. Analysis of safety parameters will be performed using this population.

- PK Population: All randomized participants who received at least 1 dose of study treatment and have at least 1 post-dose evaluable serum concentration. The PK population will be the primary population for PK analyses.

- Intensive PK Population: All randomized participants who received at least 1 dose of study treatment, and consented to participation in the Intensive PK substudy (See Current Version of Protocol) and have at least 1 post-dose evaluable serum concentration.

- PD Population: All randomized participants who received at least 1 dose of study treatment and have baseline and at least 1 post-dose evaluable PD measure. The PD population will be the primary population for PD analyses.

- Immunogenicity Population: All randomized participants who are administered any amount of study treatment and have at least 1 pre-dose evaluable ADA measure.

- Biomarker Population: All randomized participants who consented to participate in the biomarker substudy (See Current Version of Protocol). Analysis of biomarker data will be performed on the Biomarker population (analyses performed with Biomarker Population data are not included in this SAP).

- Per Protocol (PP) Population: All randomized participants with ≥ 75% compliance and without any important protocol deviations involving inclusion/exclusion criteria, study treatment, or the primary efficacy analyses. Compliance (%) is calculated by 100*(number of doses received/12). The primary efficacy analyses will be repeated for the PP population.

The PD and PK populations will be the population for the interim PK/Ig analyses (the interim PK/Ig analyses are not included in this SAP).

2.2. Protocol Deviations

Important protocol deviations will be determined by a review of the data prior to unblinding of the study results. The Sponsor or designee will be responsible for producing the final determination (ie, major vs minor) in collaboration with Veristat, prior to final study database lock.

Protocol deviations will be collected and reported at the subject level, describing the context and/or reasons for the deviations such as re-screening, use of alternative endpoint ascertainment methods, and use of alternative or rescue treatments. Additional categories related to COVID-19 may be recorded and presented in the data listing.

Important protocol deviations will be presented in a data listing.

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

The sample size for this study was calculated assuming a linear dose response (reduction of uPCR) of 0%, 15%, 30%, and 45% in placebo and VIS649 2, 4, and 8 mg/kg groups, respectively. Applying contrasts of -3, -1, 1, and 3 for the corresponding dose levels and analyzing uPCR on the natural log scale, the result is an expected mean change from baseline of 0, -0.163, -0.357, and -0.593 for placebo and VIS649 groups of 2, 4, and 8 mg/kg, respectively. Using an analysis of variance model with contrasts of -3, -1, 1, and 3 for the corresponding groups, a standard deviation (SD) of 0.87, 80% power, a 2-sided type I error rate of 0.05, and accounting for a dropout rate of ~ 20%, the required sample size is 36 participants per group, or 144 participants overall.

3.2. General Methods

All collected data will be included in listings that will contain a relative study day if there is an evaluation date. Pretreatment and on-treatment study days are numbered relative to the day of the first dose of study medication which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

All output will be incorporated into Microsoft Word Rich Text Format files sorted and labeled according to the International Council on Harmonisation recommendations and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, PK, immunogenicity, safety, and exploratory parameters. For categorical variables, summary tabulations of the number and percentage of participants within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of participants, mean, median, SD, standard error, minimum, and maximum values will be presented. For demographic continuous variables, the inter-quartile range (IQR) will also be presented.

All summary tables will be presented by treatment, including each individual VIS649 dose group, a pooled VIS649 dose group and placebo. For disposition, demographics and baseline characteristics summaries, an overall column will be included (ie, all participants).

Per study design, uPCR and eGFR measurements are collected up to Month 16. However, the treatment period is up to Month 12. Therefore, for the primary efficacy endpoint of 24-hour uPCR, the primary mixed model with repeated measures (MMRM) will include 24-hour uPCR at Months 9 and 12. For the secondary endpoint of 24-hour uPCR at 9 Months, the effect at Month 9 will be reported from the primary MMRM and included in the primary outputs. For the secondary endpoint of 24-hour uPCR at 16 Months, the same MMRM will be fitted but 24-hour uPCR at Months 9, 12 and 16 will be included (Section 4.3, 4.4).

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.4 or higher, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 24.0 or newer). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (March 2022 or newer).

3.4. Baseline Definition and Change from Baseline

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug.

Change from baseline is calculated as the difference between a participant's treatment period value and baseline period value, where t_i=any post baseline time point and t_0 is the baseline result:

$$Change\ from\ baseline = t_i - t_0$$

Percent of baseline is calculated as:

$$Percent\ (\%)\ \text{of}\ baseline = 100 * t_1/t_0$$

The percent of baseline will be analyzed for IgA, IgG, IgM, IgA1, IgA2, and Gd-IgA1 endpoints.

The change from baseline on the natural log scale is calculated as:

$$Change\ from\ baseline\ \text{on the natural log scale} = \log(t_i) - \log(t_0) = \log(\frac{t_i}{t_0})$$

The ratio change from baseline is calculated as:

$$Ratio\ change\ from\ baseline = \frac{t_i}{t_0}$$

Where t_i =any post baseline time point and t_0 is the baseline result. The change from baseline on the natural log scale and the ratio change from baseline will be analyzed for the uPCR (both Schedule A and B Urine Collection) and 24-hour urine protein excretion.

3.5. Methods of Pooling Data

Data will be pooled across sites for each group. All VIS649 participants will be pooled across VIS649 doses in addition to a by-dose presentation.

3.6. Adjustments for Covariates

Efficacy analyses will be adjusted for covariates including baseline measurements and strata.

3.7. Multiple Comparisons/Multiplicity

Formal statistical hypothesis testing will be performed on the primary efficacy endpoint of linear dose response in change from baseline in uPCR on the natural log scale at Month 12, conducted at the 2-sided, 0.048 level of significance to preserve the study-wide 2-sided type I error rate at 0.05 while accounting for interim data review (Section 4.8). The inclusion of statistical tests for secondary endpoints is intended to yield supportive evidence related to the primary objective and will be descriptive in nature as no confirmatory conclusions are intended. Statistically significant results will be examined in sequence from high dose (8 mg/kg) to low dose (2 mg/kg) compared with placebo. Tests of probability are not planned for the exploratory endpoints so that multiplicity of statistical probability test results is not a consideration.

3.8. Subgroup and Sensitivity Analyses

Subgroup analyses for primary efficacy endpoint will be performed as described in Section 4.3.2.

Sensitivity analyses will be performed as described in Section 4.3.3 for primary efficacy endpoint and in Section 4.4.2 for selected secondary efficacy endpoints.

3.9. Withdrawals, Dropouts, Loss to Follow-up

Participants who withdrew from the study, were discontinued, or lost to follow-up will not be replaced.

3.10. Missing Data

In general, there will be no imputation performed for missing data, including efficacy, safety, PK, PD, and ADA, unless otherwise specified. All data recorded on the case report form will be included in data listings that will accompany the CSR.

Missing data due to discontinuation of treatment, withdrawal from the trial or missed endpoint ascertainment will be reported at the subject level with a description of the context and/or reason for the missing data (eg, ‘COVID-19’).

For the primary efficacy endpoint, if a result is missing or not evaluable for 24-hour uPCR, and there is an unscheduled visit within 30 calendar days of the nominal visit date, the unscheduled visit assessment will be treated as the nominal timepoint.

For the analysis of AE, only partial dates will be imputed unless otherwise specified. The algorithms for imputation of partial dates depend upon the parameter, as follows:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the day of treatment.

Adverse events with missing relation will be considered related. Adverse events with missing severity will be considered severe.

For the analysis of concomitant medication, incomplete start/stop dates will be imputed based on the following imputation rules:

- If start date is completely missing, start date will not be imputed.
- If start year is present and month and day are missing, or year and day are present and month is missing, set start month and day to January 1.
- If start year and month are present and day is missing, set start day to 1st day of the month.
- If end date is completely missing, end date will not be imputed.
- If end year is present and month and day are missing, or year and day are present and month is missing, set end month and day to December 31.
- If end year and month are present and day is missing, set end day to last day of the month.
- The imputed dates must be logical, ensuring that no end date is after database lock or death or before the start date.

3.11. Visit Windows

If a participant is unable to attend a visit within 7 days of the scheduled infusion, they may still receive an infusion within the next 7 days; this will be recorded as a protocol deviation and will still be recorded for that visit. However, if there is any further delay, that dose will be skipped, and the participant will receive subsequent doses as per the schedule. The participant will not receive additional doses to make up for the missed dose(s). In data listings, all available data and the relative day of all dates will be presented.

Visits will be included in the analyses as labelled on the case report form with the exception of the following Visit/Month labels:

- M12/ET; where ET = Early Termination
- W16/EOS; where EOS = End of Study

If the 'M12/ET' visit does not occur within Days 346 - 375, relative to the first dose date, then the relative day for the visit will be determined using Table 5 and the visit label will be updated with the Month (M) of the relative day of the visit. Eg, 'ETM3' will be the visit label if the relative day of the 'M12/ET' visit was within days 76 – 105.

If the 'W16/EOS' visit does not occur within Days 454 – 492, relative to the first dose date, then the relative day for the visit will be determined using Table 5 and the visit label will be updated with the Month (M) of that relative day. Eg, 'EOSM6' will be the visit label if the relative day of the 'W16/EOS' visit was within days 166 - 195.

Table 5 Visit Windows

Visit/Month	**Relative Day**
Screening	−30 to −1
Baseline	1 (first dose date)[a]
M0	2 to 12
M0	13 to 24
M1	25 to45
M2	46 to 75
M3	76 to 105
M4	106 to 135
M5	136 to 165
M6	166 to 195
M7	196 to 225
M8	226 to 255
M9	256 to 285
M10	286 to 315
M11	316 to 345
M12	346 to 375
M13	376 to 405

M14	406 to 453
M16	454 to 492

[a] If patient has no first dose date, Day 1 will be the randomization date.

4. STUDY ANALYSES

4.1. Participant Disposition

A tabulation of the disposition of participants will be presented by group. Summaries will include the number of participants screened, failed screening, enrolled, randomized and treated, participants in each stratification factor (Japan and ROW), number of participants in each study population and number of participants who discontinued as well as the reasons for discontinuation.

A by-group, by-participant data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented. A data listing will also be presented for the inclusion/exclusion criteria not met/met, visits completed, and whether any visit was related to COVID-19.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics, including medical history, will be summarized and presented by group and overall, using the ITT population. Age, height, weight, body mass index (BMI) and baseline ECG findings will be summarized using descriptive statistics (number of participants, mean, SD, median, minimum, and maximum). The number and percentage of participants in each sex, ethnicity, race and baseline ECG interpretation category will be presented.

Baseline medical history tabulation will include whether the participant experienced any significant illnesses, pre-existing conditions or surgeries, prior tonsillectomy and prior hypertension defined by the following Preferred Term: ‘Hypertension’.

Baseline kidney biopsy history tabulation will include time since biopsy, method used for biopsy interpretation, mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis tubular, tubular atrophy/interstitial fibrosis, crescents and immunofluorescence intensity for IgA, IgG, IgM, C3, C4 and C1q.

Baseline ACEi/ARB history tabulation will include ACEi/ARB medication(s) information from the last 3 months at a minimum or previous 12 months (if known).

Baseline Systemic Immunosuppressive Agent (SIA) history tabulation will include details of any previous SIA medication use.

All demographic, baseline characteristics, medical history, kidney biopsy history, ACEi/ARB history, 12-lead ECG, serology, pregnancy, Hemoglobin A1c, and blood sample for deoxyribonucleic acid (DNA) results will be provided in data listings.

4.3. Analysis of Primary Efficacy Endpoint

Efficacy analyses will be conducted using the mITT population. The primary efficacy analyses will also be conducted on the PP population as a sensitivity analysis (See Section 4.3.3).

4.3.1. Primary Efficacy Analyses

The primary endpoint of this study is the change from baseline in uPCR (Schedule A) on the natural log scale at Month 12 (Days 360) (See Section 3.4 for change from baseline on the natural log scale equation).

A Mixed Model with Repeated Measurements (MMRM) will be used to compare the change from baseline in uPCR (Schedule A visits Months 9 and 12) on the natural log scale between treatment groups. The response variable of the MMRM is the change from baseline in uPCR (Schedule A) on the natural log scale. The model includes the fixed effects of treatment group, categorical visit (Months 9 and 12), strata and a treatment-by-visit interaction, with a fixed effect covariate of baseline uPCR (Schedule A) on natural log scale. An unstructured covariance matrix will be used. If the model does not converge, then the Toeplitz covariance structure will be used.

From the MMRM, the following statistics will be produced: 1) the least-square mean (LSM), its corresponding standard error (SE), and 95% confidence interval (CI) for each treatment group; 2) the geometric mean ratio calculated by exponentiated (LSM) and 95% CI for each treatment group; 3) the least-square mean difference (LSMD) between treatment groups using placebo as reference, its corresponding SE and 95% CI and p-value for testing the LSMD; and 4) the treatment difference expressed as geometric mean reduction calculated as (1- exponentiated LSMD) ×100%, and 95% CI.

The geometric mean reduction and corresponding SE estimated from the MMRM for each treatment group will also be presented graphically.

The alpha value for the primary efficacy analyses (ie, p-value for the test of linear contrast at Month 12) will be adjusted to account for one review of the efficacy endpoint during the interim analyses. Although the interim efficacy data reviews will not include hypothesis testing (Section 4.8.1), the type I error rate for the primary endpoint will be reduced by 0.002 for the interim efficacy review, resulting in a 2-sided type I error rate of 0.048 for the linear contrast p-value. A p-value < 0.048 for the linear contrast of the primary efficacy analysis will support a claim of efficacy.

The primary efficacy analysis result also includes the p-value from the linear contrast statement of -3, -1, 1, and 3 evaluated for VIS649 dose levels 0 (placebo), 2, 4, and 8 mg/kg, respectively at Month 12.

In addition to the linear contrast for the primary efficacy result, a quadratic contrast statement of 0.56, -0.32, -0.64, and 0.40 will also be evaluated for VIS649 dose levels 0 (placebo), 2, 4, and 8 mg/kg, respectively at Month 12 as well as a cubic contrast statement of -0.28, 0.76, -0.57 and 0.09 for VIS649 dose levels 0 (placebo), 2, 4, and 8 mg/kg, respectively at Month 12. The quadratic and cubic weights are from an R orthogonal polynomial function (R, 2020).

In addition, pairwise comparisons between the treatment groups (placebo, 2, 4, and 8 mg/kg) using different dose level as reference will be performed at Month 12. The geometric mean reduction, corresponding SEs and 95% CI for testing treatment differences will be reported. The percent change in uPCR from baseline (ie. -1(geometric mean ratio reduction)) and

corresponding SE estimated from the primary MMRM for each treatment group will be presented graphically. The p-values of pairwise comparisons between all treatment groups will also be reported.

The baseline through Month 12 MMRM will be used to compare the change from baseline in uPCR (Schedule A) on the natural log scale between the pooled VIS649 and placebo. The outputs will be similar to those estimated from the MMRM for each individual treatment group.

uPCR (Schedule A) on the natural log scale and changes from baseline will be summarized descriptively by treatment group and visit, including number and percentage of participants with missing or incomplete assessments at that visit. The raw uPCR (Schedule A), and the ratio change from baseline over time, will also be summarized over time using the geometric mean (± 95% CI).

uPCR (Schedule A and Schedule B) that is unable to be calculated because the total protein excretion is below the lower limit of quantification (LLOQ) will be reported in the statistical summaries as such. The LLOQ for the total protein excretion that is being used to calculate uPCR is [redacted] To account for individual differences due to creatinine values, values that are below the limit of quantification (BLQ) will be calculated using the imputed total protein excretion value of [redacted], divided by the participant's urine creatinine level in mg/24h for that visit. These imputed values will be included in the calculation of descriptive statistics.

In addition, the raw spot uPCR (Schedule B), and the ratio change from baseline will be summarized over time using the geometric mean (± 95% CI).

4.3.2. Subgroup Efficacy Analyses

Summary statistics for the change from baseline in uPCR (Schedule A) over time will be reported for subpopulations of participants defined by the following baseline characteristics:

- Screening uPCR (≤ 2.0 and > 2.0 g/g)
- Region (Japan and ROW)
- Baseline eGFR (30-45 and 45+ mL/min/1.73 m^2)
- Baseline Gd-IgA_1 (≤ 50^{th} and > 50^{th} percentile µg/mL)
- Baseline BMI (< 30 and ≥ 30 kg/m^2)
- Baseline Total IgA (≤ 50^{th} and > 50^{th} percentile ug/ml)
- Baseline APRIL (≤ 50^{th} and > 50^{th} percentile pg/mL)

The following subgroup analysis will be performed only if ≥ 10 participants fulfill the 'yes' category at baseline:

- ACEi/ARB therapy at enrollment (yes/no)

- Use of steroid and/or any immunosuppressive therapy prior to enrollment (yes/no)
- Tonsillectomy prior to enrollment (yes/no)
- SGLT2 inhibitor use (yes/no)
- Prior Hypertension (yes/no)

4.3.3. Sensitivity Efficacy Analyses

There will be 3 sensitivity analyses:

Sensitivity Analysis 1: the primary analysis (Section 4.3.1) performed on the PP population.

Sensitivity Analysis 2: the primary analysis (Section 4.3.1) performed on uPCR from Schedule B collections.

Sensitivity Analysis 3: the analysis of covariance (ANCOVA) model will be used to compare the treatment effects in uPCR (Schedule A) on the natural log scale between treatment groups at 12 months as a sensitivity analysis. The ANCOVA model will be fitted with treatment group, strata, and baseline uPCR (Schedule A) on the natural log scale. The outputs are the same with those estimated from the primary efficacy model for each treatment group.

4.4. Analysis of Secondary Efficacy Endpoints

Secondary analyses will be conducted using the mITT population, unless otherwise specified.

4.4.1. Secondary Efficacy Analyses

All secondary endpoints, as well as the respective changes from baseline, for each parameter will be summarized descriptively over time by treatment group, including number and percentage of participants with missing or incomplete assessments at that visit, for the following endpoints:

- 24-hour urine protein excretion (mg/day)
- eGFR (mL/min/1.73 m^2)
- Total serum IgA, IgG, and IgM concentrations (mg/dL) in the PD population

The uPCR (Schedule A; up to Month16), urine protein excretion (up to Month 16) will be summarized, at each specified time point, between placebo and VIS649 dose levels of 2, 4, and 8 mg/kg, respectively.

4.4.1.1. uPCR (from 24-hour urine collection or the intended 24-hour urine collection) at Months 9 and 16

The treatment effect for each treatment group and the treatment difference at Month 9 will be generated from the same MMRM applied in the primary efficacy analysis (Section 4.3.1). The

outputs for Month 9 are included with those from the primary efficacy analyses. The Month 16 outputs will be generated from the MMRM including Months 9, 12, and 16 (Schedule A).

4.4.1.2. 24-hour Urine Protein Excretion

The MMRMs will be fitted to estimate the treatment difference for the 24-hour urine protein excretion at Months 9, 12, and 16, respectively. Since the distribution of 24-hour urine protein excretion is skewed, the response variable will be the natural log transformed ratio of 24-hour urine protein excretion. The models will include the treatment group, strata, categorical visit, treatment-by-visit, and natural log transformed baseline 24-hour urine protein excretion as covariates. The model for Months 9 and 12 will include Baseline, Months 9 and 12. The model for Month 16 will include Baseline, Months 9, 12 and 16. The treatment differences on these assessments at Months 9, 12, and 16 will be estimated from their respective models by the differences in the geometric mean ratio reduction, along with the SEs, 95% CIs, and p-values.

24-hour Urine Protein Excretion that is unable to be calculated because the total protein excretion is below the lower limit of quantification (LLOQ) will be noted in the associated listing as such. Statistical summary tables that include imputed values will be indicated in the footnotes. The LLOQ for this test is [redacted] Values that are below the limit of quantification (BLQ) will be substituted with [redacted] for the statistical summaries and the calculation of descriptive statistics.

4.4.1.3. eGFR

MMRMs will be fitted to estimate the treatment difference for the eGFR at Months 12 and 16, respectively. The models will include the treatment group, strata, categorical visit, treatment-by-visit interaction, and baseline eGFR as covariates. The model for Month 12 will include all timepoints from baseline through Month 12. The model for Month 16 will include all timepoints from baseline through Month 16. The treatment effect on these assessments at Months 12 and 16 will be estimated by the LS means and their differences in the LS means, along with the SEs, 95% CIs, and p-values.

Change from baseline eGFR (LS mean ±SE) will be displayed graphically across time by line chart for all visits up to Month16.

4.4.1.4. eGFR Linear Slope

The eGFR linear slope from baseline to Month 12 and 16 will be derived from the slope value of a linear regression of baseline through Months 12 and 16 eGFR, respectively across time (days), per subject, using the linear model eGFR = a + b(days) where b is the linear slope value. The eGFR slope, up to Months 12 and 16, will be compared between placebo and VIS649-treated groups using an ANCOVA model with baseline eGFR as covariate.

4.4.1.5. Total serum IgA, IgG, and IgM concentrations (mg/dL) in the PD population

Total serum IgA, IgG, and IgM concentrations (mg/dL) percent of baseline and change on the natural log scale, will be summarized descriptively over time, including the geometric mean (± 95% CI). The total serum IgA, IgG, and IgM concentrations percent change and percent of baseline will be displayed graphically (mean ± SD).

4.4.1.6. Other Endpoints

The secondary efficacy analyses for the following binary endpoint will use a logistic regression model to compare VIS649 2, 4, and 8 mg/kg to placebo (0 mg/kg). Summary statistics, the odds ratio (OR), 95% CIs and p-values for each dose group (2, 4, 8 mg/kg), and pooled dose groups, compared to placebo, will be reported for the following outcomes:

- Number of participants in each group achieving a ≥ 30% decline from baseline in 24-hour uPCR (Schedule A), on the log scale, at Months 9, 12, and 16.
- Number of participants in each group achieving reduction in 24-hour urine protein excretion to < 300 mg/day for at least 3 consecutive months at Months 9, 12, and 16 if data is available.

An OR of 1 will indicate that the treatment (2, 4 or 8 mg/kg) does not affect the odds of the outcome (ie, achieving a ≥ 30% decline from baseline in uPCR (Schedule A) or achieving reduction in 24-hour urine protein excretion to < 300 mg/day or < 200 mg/mg uPCR (Schedule A) for at least 3 consecutive months at Month 12 whereas and OR > 1 will indicate that the treatment is associated with a higher odds of the outcome and an OR < 1 will indicate that the treatment is associated with a lower odds of the outcome.

4.4.2. Sensitivity Efficacy Analyses

The annualized slope of eGFR estimated over the course of 12 months. The linear mixed effects model with random effects will be used to compare the annualized slope of eGFR between treatment groups estimated over the course of 12 months. The response variable of the model is the eGFR value at each post baseline visit. The model will be fitted with fixed effects of treatment, time (as a continuous variable), treatment-by-time interaction, strata, baseline eGFR and random effects of intercept and time. The unstructured covariance structure will be used. The annualized eGFR slope by each treatment group, together with SE and 95% CI will be reported. The statistical inference will be based on testing of the difference on the eGFR annualized slope between two treatment groups and estimation of the difference and its 95% CI.

4.5. Analyses of Exploratory Endpoints

[redacted]

All exploratory endpoints (see Section 1.2.5.3), excluding those specified to be analyzed outside of this SAP, as well as the respective changes from baseline, for each parameter will be summarized descriptively over time by treatment group, including number and percentage of

participants with missing or incomplete assessments at that visit. No formal statistical comparisons will be performed.

4.6. Other Analyses

Pharmacokinetic analyses will be conducted using the PK Population. Population PK/PD analysis will be analyzed outside of this SAP and will be reported separately.

4.6.1. Pharmacokinetic Concentrations

Individual and descriptive summaries of VIS649 serum concentrations by timepoint and dose will be provided. Figures of individual serum concentration-time profiles of VIS649 will be created, where the actual time will be plotted on the x-axis.

For participants in the intensive PK population (See current version of Protocol Version for details of the PK substudy) at Months 0 and 11, mean and median concentration time profiles will be calculated by dose and plotted on linear and semi-log scales at Months 0 and 11. The mean profiles will include standard deviation. The number of values above the lower limit of quantification (LLOQ) will be reported in the statistical summaries. Values that are below the limit of quantification (BLQ) will be substituted with zero for the calculation of descriptive statistics of concentration by time point. Missing samples will be reported as no sample ("NS") and excluded from the statistical summaries.

Samples with no actual date and time collected will be excluded from the analysis. No formal statistical comparisons will be performed.

4.6.2. Pharmacokinetic Parameters

Pharmacokinetic parameter analyses will be conducted using participants from the PK Population or Intensive PK Population.

VIS649 serum concentrations for participants in the intensive PK Population will be analyzed using standard noncompartmental methods. Serum concentration values below the LLOQ will be set to 0 before the peak concentration and set to missing after the peak concentration in the PK evaluation. Individual and summary PK parameters (outlined in Table 4) will be listed by dose, visit (ie, Month 0 or Month 11) and subject. No formal statistical comparisons will be performed.

4.6.3. Immunogenicity Evaluations

Anti-VIS649 ADA analyses will be conducted using the Immunogenicity population.

Individual ADA results will be listed by subject and the tabular summarization of ADA results will include the number and proportion of subjects with positive pre-dose ADA response, number/proportion of subjects with positive post-dose ADA response only, and number/proportion of subjects with positive ADA response at any time. The following immunogenicity endpoints will be summarized by group, dose and time point using descriptive statistics.

- Results of a confirmatory ADA assay (positive/negative)
- ADA titers for participants with a positive confirmatory assay
- Results of a neutralizing ADA assay (positive/negative)

No formal statistical comparisons will be performed.

4.7. Analyses of Safety Endpoints

Safety analyses will be conducted using the Safety Population and will be summarized by the treatment participants receive.

4.7.1. Study Drug Exposure

The duration of drug exposure and compliance will be calculated as specified below and will be summarized by group using descriptive statistics. Duration of drug exposure, compliance and number of doses received for each participant will also be provided in a data listing, flagging participants who withdrew from the study early. In addition, the dose modification (eg, dose interruption during an infusion, missing infusions, et al.), including number of subjects with at least one dose interruption and reasons for interruption will be summarized. A dose is received when there is ≤ 5mL total volume remaining in the bag after infusion.

Duration of Exposure = Last Dose Date - First Dose Date + 30 Days

Compliance = Number of Doses Received/12

Percent Compliance = 100(Number of Doses Received/12)*

4.7.2. Adverse Events

All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using system organ class and preferred term (PT). Severity is assigned by the investigator as mild, moderate or severe.

Analyses of AEs will be performed for those events that are considered treatment-emergent, defined as any AE with an onset date on or after the start of study treatment, including any events that worsen in severity after the start of treatment.

AEs are summarized by incidence rates; therefore, in any tabulation, a subject contributes only once to the count for a given AE or system organ class. For tabulations by maximum severity, participants will be counted only once for the most severe occurrence of the AE or system organ class.

A summary of AEs will include the number and percentage of participants who experience at least one of the following:

- Treatment-Emergent Adverse Events (TEAEs)
- Treatment-Related TEAEs

- Severe TEAEs
- Severe Treatment-Related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- Treatment-Related TEAEs Leading to Study Drug Interruption
- Treatment-Related TEAEs Leading to Study Drug Discontinuation
- Treatment-Related TEAEs Leading to Death

The above categories will be presented by system organ class and PT. In these tabulations, a subject contributes only once to each of the incidence rates for a given system organ class or PT, regardless of the number of episodes, by highest severity or closest relationship.

Additional tabular subgroup presentations of TEAEs by System Organ Class and PT will be included as follows:

- TEAEs by concomitant medication with a frequency of use of ≥ 5% of the participant population during the Treatment Period
- Treatment-Related TEAEs by concomitant medication with a frequency of use of ≥ 5% of the participant population during the Treatment Period
- Serious Adverse Events by concomitant medication with a frequency of use of ≥5% of the participant population during the Treatment Period
- TEAEs for participants with comorbidities occurring in 5% or more of overall participants by Treatment Group
- TEAEs by Maximum Severity
- Treatment-Related TEAEs by Maximum Severity

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on-study (including the screening period) will be listed in by-subject data listings, with a flag indicating treatment emergence.

4.7.3. Laboratory Data

Clinical laboratory values will be expressed using the Conventional Units and graded using Common Terminology Criteria for Adverse Events (CTCAE) criteria for applicable parameters.

The actual value and change from baseline (Day 1 Pre-infusion) to each on-study evaluation and to the last evaluation on study will be summarized for each clinical laboratory parameter,

including hematology, chemistry, and urinalysis. In the event of repeat values, the last non-missing value per study day will be used.

Tables presenting shift in CTCAE grade from baseline to worst and baseline to last on-study values may be presented for applicable hematology and clinical chemistry parameters.

All laboratory data will be provided in data listings. A data listing will be presented for all abnormal laboratory values.

4.7.4. Vital Signs and Physical Examination

The actual value and change from baseline (Day 1 Pre-infusion) to each on-study evaluation will be summarized for vital signs.

Vital signs will include a derived measurement of Mean Arterial Pressure (MAP):

MAP = Diastolic Pressure+1/3(Systolic Pressure-Diastolic Pressure)

Where pressure = blood pressure (mm Hg).

The number and percentage of participants who experience a clinically significant vital sign post -baseline will be summarized. Clinically significant vital signs will be summarized as follows (increases and decreases are from baseline):

- Systolic Blood Pressure (SBP) < 90 mmHg and Decrease ≥ 20 mmHg
- SBP > 180 mmHg and Increase ≥20 mmHg
- Diastolic Blood Pressure (DBP) < 50 mmHg and Decrease ≥ 10 mmHg
- DBP > 105 mmHg and Increase ≥ 10 mmHg
- SBP ≥ 140 mmHg and DBP ≥90 mmHg
- Heart Rate (HR) < 50 bpm and Decrease ≥ 15 bpm
- HR > 120 bpm and Increase ≥ 15 bpm

Vital sign measurements will be presented for each participant in a by-group by-participant data listing where results meeting the above clinically significant criteria will be identified.

4.7.5. Prior and Concomitant Medications

The prior and concomitant medications or therapies will be coded using the most current available version of World Health Organization (WHO) Drug Dictionary Enhanced (March 2022 or newer) by therapeutic class and drug name.

Prior medications or therapies are defined as any medications or therapies administrated prior to the first dose of study treatment. Concomitant medications or therapies are defined as those administrated on or after the date of the first dose of study treatment.

Prior and concomitant medication or therapies will be summarized in each treatment group by each medication within each therapeutic class for the Safety population. If a subject has a specific medication or therapy multiple times or takes multiple medications or therapies within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class. However, all prior and concomitant medications or therapies will be included in listings.

A tabular presentation of concomitant medications (during the Treatment Period) will be included for medications taken by ≥ 5% of the participant population.

COVID-19 vaccinations will be tabulated by group separately.

4.8. Interim Analyses

Group-unblinded summaries will be prepared for Sponsor review to inform on future study design, no modifications to this study protocol are planned based on results of the interim analyses. Individual participant treatment will be blinded in all interim outputs. The interim outputs will be prepared by a separate, unblinded team.

4.8.1. Interim Efficacy and Safety Analyses

The interim analyses will include disposition, efficacy and safety analysis. The interim analyses will be performed on the mITT population and will be performed once 50% of randomized participants have 9-month uPCR (Schedule A). All randomized participants will be included in the interim analysis.

Both blinded and unblinded interim analysis outputs will be produced where the unblinded outputs will only be made available to unblinded team members.

For the interim efficacy outputs, the uPCR (Schedule A), uPCR on the natural log scale, change from baseline in uPCR on the natural log scale, and ratio change from baseline in uPCR values will be summarized descriptively over time by treatment group, including number and percentage of participants with missing or incomplete assessments at that visit. The uPCR geometric mean (± SD) ratio change from baseline at Month 9 for VIS649 individual treatment groups and pooled treatment group will be also displayed graphically. In addition, the raw spot uPCR (Schedule B) and the ratio change from baseline over time will be presented over time using the geometric mean (95% CI) of the raw and ratio change values by summary and plot.

The 24-hour uPCR (Schedule A) model at Month 9 will be an ANCOVA model for change from baseline on the natural logarithmic scale of uPCR at Month 9, including the covariate of baseline uPCR on the natural logarithmic scale, in addition to the fixed effect of strata. The exponentiated LSMs, SE, and 95% CI for the treatment groups will be reported at Month 9. Similar ANCOVA model will be applied for pooled VIS649 treatment vs. placebo.

In the interim efficacy analyses, the hypothesis testing will not be included. Nonetheless, to account for the review of the efficacy endpoint, the type I error rate applied to the primary

analyses, at the end of the study, will be reduced by 0.002 for the interim efficacy review, resulting in a 2-sided end-of-study type I error rate of 0.048 (See Section 3.7).

The 24-hour urine protein excretion, change from baseline and change from baseline on the natural log scale will be summarized descriptively over time by treatment group, including number and percentage of participants with missing or incomplete assessments at that visit.

The eGFR and change from baseline will be displayed graphically over time by line chart for all available visits.

The interim safety analyses will include a summary of AEs (number and percentage of participants) for overall who experience at least one of the following:

- TEAEs
- Treatment-Related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- Treatment-Related TEAEs Leading to Study Drug Interruption
- Treatment-Relate TEAEs Leading to Discontinuation of Study Drug
- Treatment-Related TEAEs Leading to Death
- CTCAE Grade ≥ 3 TEAEs

The above categories will be presented by system organ class, PT, and either maximum severity or maximum CTCAE grade. In these tabulations, a subject contributes only once to each of the incidence rates for a given system organ class or PT, regardless of the number of episodes, by highest severity or closest relationship.

4.8.2. Interim PK/Ig Analyses

Three interim PK/Ig analyses will be performed on the PK and PD populations, which will be described in a separate analysis plan.

5. CHANGES TO PLANNED ANALYSES

This document is amended after the formal efficacy interim analyses as outlined in Section 4.8. Sponsor was unblinded to the group summary of the efficacy interim results.

Additional analysis populations, secondary and exploratory endpoints and time points for analyses are included in this SAP.

The major change between protocol and this SAP is summarized below:

1. There are 2 planned interim efficacy analyses in the protocol. Sponsor chose not to perform the interim efficacy 1 during the trial. In this SAP, Section 4.8.1 is updated to reflect the new scope and analysis method for the interim efficacy analysis.

All other changes from procedures outlined in this SAP will be summarized in the study report.

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7. REVISION HISTORY

Revision	Date	Revision Summary
2.0	27-September-2021	• Percent change from baseline formula corrected to: (tit0)/t0. • Duration of treatment exposure formula changed to: last dose date – first dose date + 30 days
3.0	29-March-2022	• Update the Section 4.8.1 Interim Efficacy Analysis. • Update the Section 4.8.2 Interim PK/Ig Analyses • Delete the Table 14.2.1.5, 14.2.1.6, 14.2.1.8, and 14.2.1.9 for Interim Efficacy Analysis since the Interim Efficacy Analysis shell will be a separate document. • Update the Section 4.7.1 Study Drug Exposure to add the description of dose modifications. • Add the Table 14.1.10 for dose modifications • Update the Section 5 to add changes to planned analyses in Protocol. • Remove references to the Operational Plan • Update the Section 1.2.1 Synopsis of Study Design • Update the Section 8.1
4.0	3-March-2023	• Updated Primary Efficacy Analysis • Updated Secondary Efficacy Analysis • Updated Visit Windowing • Updated Change from Baseline Definitions. • Updated a-g IgA1 to Gd IgA1 • Updated exploratory objectives to be analyzed outside of this SAP • Updated Exploratory Endpoints • Addition of Intensive PK Population • Update Per Protocol Population Definition • Update concomitant medication imputation for missing/incomplete start and end dates. • Update Subgroup Efficacy Analyses • Update Sensitivity Efficacy Analyses • Addition of neutralizing ADA assay (positive/negative) endpoint • Update tabular subgroup presentations of TEAEs • Update definitions for prior and concomitant medications • Update internal links and TOC

4.0	10-March-2023	• Update header footer for date stamp
5.0	27-Jun-2023	• Updated Primary Efficacy Analysis • Updated Secondary Efficacy Analysis • Updated Sensitivity Efficacy Analysis • Update header for date stamp • Addition of visit windowing for uPCR Schedule A collections • Addition of imputation for uPCR where protein is at BLQ