STATISTICAL ANALYSIS PLAN

Visterra Inc.

VIS649-101

A Phase 1, Randomized, Placebo-Controlled, Single Ascending Dose First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of VIS649 Administered Intravenously in Healthy Subjects

REVISION HISTORY

Version	Version Date
Final 1.0	3 Jun 2019

SIGNATURE PAGE – VISTERRA INC.

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
ADA	Anti-drug Antibody
AE	Adverse event
a-g IgA	Aberrantly glycosylated IgA (synonymous with GD IgA)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
APRIL	A proliferation inducing ligand
aPTT	Activated partial thromboplastin time
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
$AUC_{0\text{-}112d}$	Area under the concentration-time curve from pre-dose (time 0) to the concentration on day 112
$AUC_{0\text{-}inf}$	AUC from time zero extrapolated to infinity
$AUC_{0\text{-}last}$	AUC from time zero extrapolated to the last quantifiable concentration
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per minute
BUN	Blood urea nitrogen
°C	Centigrade
CI	Confidence interval
CL	Clearance calculated as: Dose/$AUC_{0\text{-}inf}$
CSP	Clinical Study Protocol
C_{max}	Maximum observed concentration
CS	Clinically significant

Abbreviation / Acronym	Definition / Expansion
CV	Coefficient of variation
D	Day
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FIH	First In Human
gCV	Geometric coefficient of variation
GGT	Gamma glutamyl transferase
GMR	Geometric mean ratio
H	Above the upper limit
Hb	Hemoglobin
HCT	Hematocrit
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
ICD	Informed consent document
ID	Identification
Ig	Immunoglobulin
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IV	Intravenous
L	Below the lower limit

Abbreviation / Acronym	Definition / Expansion
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
n	Number of subjects
N/A	Not applicable
NC	Not calculable
NCS	Not clinically significant
NK	Not known
NS	No sample
OTC	Over-the-counter
PD	Pharmacodynamic
PK	Pharmacokinetic
PROC	Procedure
PT	Preferred Term
QTcF	QT-interval corrected using the Fridericia's correction
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SOC	System Organ Class
SQRT	Square root

Abbreviation / Acronym	Definition / Expansion
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TLFs	Tables, Listings and Figures
t_{max}	Time corresponding to occurrence of C_{max}
V_d	Volume of distribution calculated as: CL/λz
vs.	Versus
W	Week
WBC	White blood cell
WHODrug	World Health Organization - Drug
λ_z	Terminal elimination rate constant

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the CSP Amendment 2, Version 3.0 (Final), dated 12 Mar 2019. The SAP will be updated as required by protocol amendment or trial insights, and finalized prior to database lock. The document describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

1. STUDY OBJECTIVES

1.1 Primary Objective

To evaluate the safety and tolerability of VIS649 in healthy subjects

1.2 Secondary Objectives

- To characterize the pharmacokinetic (PK) profile of VIS649
- To evaluate the effect of ethnicity on the PK profile of a single intravenously (IV) administered dose of VIS649 in healthy Japanese and non-Japanese subjects
- To characterize the levels of anti-drug antibodies
- To characterize the effect of VIS649 on pharmacodynamic (PD) parameters including:
    - changes in serum total IgA, IgG and IgM concentrations and time to recovery.
    - changes in circulating lymphocyte populations in cohorts 1-4 only (this assessment will be done for all lymphocytes, and also for lymphocyte subsets that are noted to show changes from baseline)

- To assess ADA status impact on VIS649 PK parameters

[redacted]

2. ENDPOINTS

2.1 Primary Endpoint

- Safety Endpoint
  - The proportion of subjects with AEs and serious adverse events (SAEs) following administration of VIS649; safety will be assessed from the time of study drug administration to the end-of-study participation.
  - The following safety variables will be collected and recorded at regular intervals during the study:
    - Adverse event assessments
    - Clinical laboratory tests (hematology, clinical chemistry and urinalysis)
    - Vital signs (sitting BP, heart rate, temperature and respiratory rate [RR])
    - Twelve-lead ECG
    - Adjunctive procedures
    - Physical examination

2.2 Secondary Endpoints

- Characterization of anti-drug antibodies (ADA) levels

2.2.1 Pharmacokinetics Endpoints

The following PK parameters for VIS649 will be determined, as appropriate:

- C_{max}: Maximum serum VIS649 concentration determined directly from the concentration-time profile
- T_{max}: Time of maximum serum VIS649 concentration determined directly from the concentration-time profile
- AUC $_{0\text{-}112d}$: Area under the concentration-time curve from pre-dose (time 0) to the concentration on day 112
- AUC $_{0\text{-}last}$: Area under the concentration-time curve from pre-dose (time 0) to the last quantifiable concentration
- $AUC_{0\text{-}inf}$: Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinite time [redacted]
- $t_{1/2}$: Terminal elimination half life
- Vd: Volume of distribution [redacted]
- CL: Clearance [redacted]

2.2.2 Pharmacodynamic Endpoints

- Changes in total serum IgG, IgA and IgM concentrations and time to recovery
- Changes in circulating lymphocyte populations in cohorts 1-4 only (this assessment will be done for all lymphocytes, and also for lymphocyte subsets that are noted to show changes from baseline).
- [redacted]

[redacted]

3. STUDY DESIGN

3.1 Study Design

This is a phase 1, randomized, placebo-controlled, double-blind, and single ascending dose study to investigate the safety, tolerability, PK/PD of the IV administration of VIS649 in healthy subjects.

The study will be conducted in five sequential dosing cohorts. Cohorts 1-4 will enroll 9 subjects per cohort. Cohorts 1-4 will enroll 4 Japanese subjects and will be randomized to VIS649 or placebo in a ratio of 7:2 (7 active, 2 placebo). The fifth cohort will enroll up to 15 subjects with targeted but non-mandatory enrollment of up to 5 Japanese subjects. The subjects in cohort 5 will be randomized to VIS649 or placebo in a ratio of 10:5 (10 active, 5 placebo). In addition, all subjects in cohort 5 will receive TENIVAC® vaccine.

Sentinel subjects will be utilized in cohorts 1-4 (but not in cohort 5); the first two subjects in each cohort will be randomized to receive either VIS649 (n=1) or placebo (n=1) and will receive study drug at least 24 hours before the remaining subjects in the cohort (7 subjects) are dosed. These 2 subjects shall remain confined to the study center for 24 hours after study drug administration. Cohort 5 does not require sentinel subjects as the dose of VIS649 has already been evaluated in cohort 3.

The Schedule of Assessments is listed in Table 1.

Table 1 Schedule of Assessments

Activity	Screen	Base - line	Post-Dosing Period Assessments															Additional Visits[7]	
Time Point (Day)	**Days -28 to -1**	**BL D-1 pre-dose**	**D1**	**D2**	**D3**	**W1/ D7**	**W2/D 14**	**W3/D 21**	**W4/D 28**	**D31[9]**	**W5/ D35**	**W6/ D42**	**W7/ D49 (cohorts 1-4 only)**	**W8/ D56**	**W10/ D70**	**W12/ D84**	**W14/ D98**	**W16/ D112**	**W 20**	**W24**
+/- visit allowance	**N/A**	**N/A**	**N/A**	**N/A**	**+1**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-5**	**+/-5**
In-house Day		x	x	x[1]																
Ambulatory Visit	x				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[2]	x[2]
Procedures																				
Informed Consent/HIPAA	x																			
Verify Inclusion/ exclusion criteria	x	x																		
Demographics & Medical History	x																			
Pregnancy Test (Serum β-hCG)	x																	x		
Pregnancy Test (urine dip stick)		x																		
Serology - HBsAG, Hepatitis C, HIV-test	x																			
Drug & alcohol toxicology screen	x	x																		
Physical Examination - Full	x	x																		
Physical					x				x					x		x		x		

Activity	Screen	Base - line	Post-Dosing Period Assessments																Additional Visits[7]	
Time Point (Day)	**Days - 28 to -1**	**BL D-1 pre-dose**	**D1**	**D2**	**D3**	**W1/ D7**	**W2/D 14**	**W3/D 21**	**W4/D 28**	**D31[9]**	**W5/ D35**	**W6/ D42**	**W7/ D49 (cohorts 1-4 only)**	**W8/ D56**	**W10/ D70**	**W12/ D84**	**W14/ D98**	**W16/ D112**	**W 20**	**W24**
+/- visit allowance	**N/A**	**N/A**	**N/A**	**N/A**	**+1**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-5**	**+/-5**
Examination - Brief																				
Vital Signs[3]	x	x	x		x	x	x		x					x		x		x		
ECG	x	x	x[4]																	
Concomitant Medications	x	x	x		x	x	x	x	x		x	x		x	x	x	x	x	x	x
AE Check		x	x	x	x	x	x	x	x		x	x		x	x	x	x	x	x	x
IV Study Infusion			x																	
Laboratory Assessments																				
Serum Chemistry / Coagulation	x	x			x		x													
Urinalysis	x	x			x				x					x				x		
Hematology (CBC with differential)	x	x			x		x		x					x		x				
Blood Sampling for PK[5]			x[5]	x[5]	x	x	x		x[10]			x		x	x			x		
Blood Sampling for PD (Immunoglobulins)	x	x			x	x	x	x	x[10]		x	x	x	x	x	x		x	x	x
Blood Sampling for Ig subtypes		x				x			x[10]					x		x		x		
Blood Sampling		x							x									x	x	x

Activity	Screen	Base - line	Post-Dosing Period Assessments																Additional Visits[7]	
Time Point (Day)	Days -28 to -1	BL D-1 pre-dose	D1	D2	D3	W1/ D7	W2/D 14	W3/D 21	W4/D 28	D31[9]	W5/ D35	W6/ D42	W7/ D49 (cohorts 1-4 only)	W8/ D56	W10/ D70	W12/ D84	W14/ D98	W16/ D112	W 20	W24
+/- visit allowance	N/A	N/A	N/A	N/A	+1	+/-1	+/-3	+/-3	+/-3	+/-1	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-5	+/-5
for PD (lymphocyte populations)[8]																				
[redacted]																				
Blood sampling for ADA		x							x[10]					x				x	x[7]	x[7]
Vaccine Administration[9, 10]									x											
Tetanus/diphtheria serology[9, 10]									x[10]	x	x	x		x		x		x		

Abbreviations: ADA: Anti-drug Antibody; AE: Adverse event; D: Day; ECG: Electrocardiogram; HBsAG: Hepatitis B surface antigen; HIPAA: Health Insurance Portability and Accountability Act; HIV: Human Immunodeficiency Virus; Ig: Immunoglobulin; IV: Intravenous; N/A: Not Applicable, PD: Pharmacodynamics; PK: Pharmacokinetics; W: Week.

1. The first two subjects of each cohort will be discharged 24 hours (Day 2) after the study infusion. All other subjects are discharged on Day 2, 24 hours after study infusion. Discharge from the Phase 1 unit will not occur prior to performing the 24 h post infusion study procedures.

2. Optional Visit at Week 20 is only to be made if immunoglobulin levels (IgG, IgM, or IgA) have not returned to normal range by Week 16; the Optional Visit at Week 24 is only to be made if immunoglobulin levels have not returned to normal range by Week 20. If immunoglobulin levels (IgG, IgM, or IgA) have not returned to normal range by Week 16 for one or more subjects, the entire cohort will complete Week 20 and Week 24.
3. Vitals signs at Screening and Day -1 will include height and weight, to permit estimated creatinine clearance calculation, as well as blood pressure (bp), heart rate (hr), respiratory rate (rr) and temperature. Subject weight will be measured after admission to the research unit (Day -1) and will be used by pharmacy staff for subject-specific dose calculation. Vital signs at other timepoints will be limited to temperature (Day -1 and Day 1 pre-dose only), bp, hr, and rr. Vital signs measurements on Day 1 will be recorded within 30 minutes prior to the start of the infusion, then every 15 minutes until the infusion is complete and post infusion at 60 minutes, 2 hours and 4 hours. On subsequent visits, vital signs will be recorded, as possible, at approximately the same time of day, if convenient. Post-dose bp should be based on the end of infusion time.
4. On Day 1 electrocardiograms will be done within 30 minutes prior to infusion and at the end of the infusion (+10 min).
5. On the day of study infusion (Day 1), blood samples for PK analysis will be collected prior to start of the infusion, at the end of infusion (60 minutes), and at 2 hours, 8 hours, and 24 hours post end of infusion. All subjects will have PK samples drawn on Days 3, 7, and Weeks 2 (Day 14), 4 (Day 28), 6 (Day 42), 8 (Day 56), 10 (Day 70), and 16 (112).

[redacted]

7. This sampling will not be done for cohort 5.

[redacted]

9. This sampling will be pre-vaccination in cohort 5.

Cohorts are planned as follows:

Table 2 Cohorts and Dose Administration

Cohorts	Number of Subjects	Treatment
Cohort 1	N=7	VIS649 0.5 mg/kg
	N=2	Placebo
Cohort 2	N=7	VIS649 2.0 mg/kg
	N=2	Placebo
Cohort 3	N=7	VIS649 6.0 mg/kg
	N=2	Placebo
Cohort 4	N=7	VIS649 12 mg/kg
	N=2	Placebo
Cohort 5	N=10	VIS649 6.0 mg/kg plus vaccine
	N=5	Placebo plus vaccine

3.2 Study Population

A total of 51 healthy Japanese and non-Japanese male and female subjects will be enrolled in this clinical study. Cohorts 1-4 may have up to 36 subjects enrolled (a total of up to 16 Japanese subjects and up to 20 non-Japanese subjects). Cohort 5 may have up to 15 subjects (N=15) with a targeted but non-mandatory enrollment of up to 5 Japanese subjects. Detailed lists of inclusion and exclusion criteria are shown in Sections 4.2 and 4.3 of the CSP.

3.3 Statistical Basis for Sample Size

The sample size for this FIH Phase 1 study was not based on formal statistical determinations. The sample size for this study was chosen in consideration of limiting exposure to this new chemical entity while providing sufficient information to evaluate the safety and tolerability of VIS649 in a Phase I setting.

3.4 Randomization

Randomization and blinding will occur according to a core randomization list administered by the site's unblinded pharmacist.

Prior to dosing on Day 1, all screened and eligible subjects will be assigned a randomization number in accordance with the randomization code generated by PAREXEL International. If subjects are withdrawn prematurely from the study and are replaced under the direction of the Sponsor, then a replacement randomization number will be assigned. Cohort, randomization numbers and replacement numbers are listed in Table 3.

Table 3 Randomization Numbers and Treatment Assignment

Dose Group	Randomization Numbers	Replacement Numbers	Treatment Assignment	
Cohort 1	[redacted]	[redacted]	0.5 mg/kg VIS649 (N=7)	Placebo (N=2)
Cohort 2	[redacted]	[redacted]	2.0 mg/kg VIS649 (N=7)	Placebo (N=2)
Cohort 3	[redacted]	[redacted]	6.0 mg/kg VIS649 (N=7)	Placebo (N=2)
Cohort 4	[redacted]	[redacted]	12 mg/kg VIS649 (N=7)	Placebo (N=2)
Cohort 5	[redacted]	[redacted]	VIS649 6.0 mg/kg plus vaccine (N=10)	Placebo plus vaccine (N=5)

No more than one Japanese subject per cohort may be randomized to receive placebo in cohorts 1-4. No more than two Japanese subjects may be randomized to receive placebo in cohort 5.

3.5 Subject Withdrawal and Replacement

All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge. Subject participation may be terminated prior to completing the study and the reason recorded as follows:

- Adverse event
- Protocol violation
- Loss to follow-up
- Subject withdrew consent at own request

- Other

Once a randomization number has been allocated to one subject, it may not be assigned to another subject. If subjects withdrawn prematurely from the study and are replaced under the direction of the Sponsor, then a replacement randomization number will be assigned. A replacement randomization code will be generated such that replacement subjects are assigned to the same treatment as the discontinued subjects. The replacement randomization code will differ only in randomization numbers, which will be 4-digit numbers [redacted]

3.6 Termination of the Clinical Study

The clinical study may be terminated at the Sponsor's discretion also in the absence of such a finding. Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant or unacceptable risk to the subjects enrolled in the clinical study;
- Failure to enroll subjects at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the study drug.

4. STATISTICAL ANALYSIS CONVENTIONS

4.1 Analysis Variables

4.1.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded:

- Date of informed consent
- Age
- Ethnicity: Japanese, Non-Japanese (Hispanic, Latino, Caucasian, etc.)
- Race: White, Black or African American, Asian, American Indian and Alaska Native, Native Hawaiian and Other Pacific Islander

- Height, without shoes (cm)
- Body weight, without shoes (kg)
- BMI (kg/m^2)
- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- History of blood or plasma donation

Medical History includes:

- General medical history
- Medication history
- Reproductive history

All medical history will be coded using Version 21.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

4.1.2 Concomitant Medication

Any medicinal product, prescribed or OTC, including herbal and other nontraditional remedies, is considered a concomitant medication. Prior and concomitant medication use will be recorded for the 30 days prior to the Screening Visit until the End-of-Study Visit.

Complete or partial dates will be handled as follows:

- Medication with completely missing start date will be considered as prior.
- Medication with a partial start date will be considered as prior unless the available portion of the date indicates otherwise.
- Medication with a missing start time where the start date is the same as the dosing date will be considered as prior.

- Medication with completely missing end date will be considered as concomitant.
- Medication with a partial end date will be considered as concomitant unless the available portion of the date indicates otherwise.
- Medication with a missing end time and end date that is the same as the dosing date will be considered as concomitant.

Medications with missing date and/or time information will have the missing information identified by NK in the listings (where NK = Not Known).

Concomitant medication will be coded using the World Health Organization-Drug Dictionary (WHO Drug Version Global September 2018 B3) and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

4.1.3 Exposure to the Investigational Medicinal Product (IMP)

Data of study drug administration will be recorded, including the infusion date, start and stop times of the infusion, total volume infused, site of infusion, and arm used.

For cohort 5 participants, an additional single dose of tetanus/diphtheria vaccine will be injected intramuscularly into the opposite arm of the one with study drug administration, its administration data will be collected.

4.1.4 Safety Variables

4.1.4.1 Adverse Events

Adverse event reporting will begin for each subject from Baseline (Day -1) and will continue until the End-of-study Visit. All serious adverse events (SAEs) will be recorded from signing of the ICD until the End-of-study Visit.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

The Principal Investigator will assess all AEs for severity in accordance with the standard ratings: Mild, Moderate and Severe. Details can be found in the section 6.2.1.3.1 of the CSP.

The Principal Investigator will assess the causality/relationship between the study drug and the AE based on the categories of Related, Probably related, Possibly related, Unlikely to be related, and Unrelated. The causality for each AE will be summarized as "related" (Related, Probably related, and Possibly related) and "not related" (Unlikely to be related, and Unrelated). Details are described in the section 6.2.1.3.2 of the CSP.

AEs for cohort 5 will be assessed for relationship to vaccine and its administration separately from relationship to study drug and its administration (see sections 1.3 and 6.2.1.3 of the CSP for details).

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 or higher.

4.1.4.2 Clinical Laboratory Tests

The following safety laboratory parameters will be measured (Table 2) in the study.

Table 4 Clinical Laboratory Assessments

Hematology	
White blood cell (WBC) count	Neutrophils (percentage and absolute count)
Red blood cell (RBC) count	Lymphocytes (percentage and absolute count)
Hemoglobin (Hb)	Monocytes (percentage and absolute count)
Hematocrit (HCT)	Eosinophils (percentage and absolute count)
Mean corpuscular volume (MCV)	Basophils (percentage and absolute count)
Mean corpuscular hemoglobin (MCH)	Platelet count
Mean corpuscular hemoglobin concentration (MCHC)	RBC distribution width
Coagulation	
Prothrombin time (PT)	International Normalized Ratio (INR)
Activated partial thromboplastin time (aPTT)	
Clinical Chemistry	
Alanine aminotransferase (ALT)	Glucose
Albumin	Lactate dehydrogenase (LDH)
Alkaline phosphatase (ALP)	Phosphorus
Aspartate aminotransferase (AST)	Potassium
Blood urea nitrogen (BUN)	Sodium
Calcium	Total bilirubin
Chloride	Total protein
Cholesterol	Triglycerides
Creatinine	Uric acid

Gamma glutamyl transferase (GGT)	FSH (Screening Visit only; all female subjects)
Urinalysis	
Bilirubin	Blood
Glucose	pH and specific gravity
Ketones	Protein
Leukocytes	Urobilinogen
Nitrite	Microscopic (only for abnormal urine stick test findings)
Viral Serology	
Human immunodeficiency virus (HIV) (Types 1 and 2) antibodies	Hepatitis C virus antibody (anti-HCV)
Hepatitis B surface antigen (HBsAg)	
Serology	
Tetanus/diphtheria serology	
Urine Drug Screening and Cotinine Test	
Amphetamines	Cocaine
Barbiturates	Opiates
Benzodiazepines	Phencyclidine
Cannabinoids	Cotinine
Urinary creatinine (to exclude dilution effect)	Ethanol
Pregnancy Testing	
Serum/urine human beta chorionic gonadotrophin (women of childbearing potential only)	

4.1.4.3 Vital Signs

The following vital signs measurements will be obtained at the time points detailed in the Schedule of Assessments in Table 1.

- Systolic blood pressure (SBP) [mmHg]
- Diastolic blood pressure (DBP) [mmHg]
- Heart Rate (bpm)
- Respiratory rate (breaths per minute)
- Temperature [°C]

Blood pressure and heart rate recordings will be made after the subject has been in a seated or supine position and at rest ≥ 5 minutes.

4.1.4.4 Standard 12-lead Electrocardiograms

12-lead ECGs will be performed at the time points detailed in the Schedule of Assessments in Table 1. The following ECG parameters will be recorded:

- RR-interval (msec)
- PR (PQ)-interval (msec)
- QRS-duration (msec)
- QT-interval (msec)
- QT-interval corrected using the Fridericia's correction (QTcF) (msec)
- Heart rate (HR) (beats per minute [bpm])

The 12-lead ECGs will be performed after the subject has been resting supine for≥ 5 minutes.

All ECGs must be evaluated by a qualified physician as "Normal", "Abnormal, NCS" or "Abnormal, CS", the abnormalities will be presented.

4.1.4.5 Physical Examination

The full physical examinations and brief physical examinations will be conducted by a licensed physician in accordance with the Schedule of Assessments in Table 1. The details of the full/brief physical examinations are described in the section 6.2.5 of the CSP.

4.1.5 Pharmacokinetic Variables

Blood samples for the determination of the concentration of VIS649 will be collected on Day 1 (prior to the start of infusion, at the end of infusion (60 minutes) and at 2 hours, 8 hours and 24 hours post end of infusion), Days 3, 7, 14, 28, 42, 56, 70, and 112. For details please refer to the Schedule of Assessments in Table 1.

The following PK parameters will be determined for VIS649 in serum samples following single dose administration:

Table 5 Pharmacokinetic Parameters after Single Dose Administration

Parameter	Definition
C_{max}	Maximum serum VIS649 concentration determined directly from the concentration-time profile
T_{max}	Time of maximum serum VIS649 concentration determined directly from the concentration-time profile
$AUC_{0\text{-}112d}$	Area under the concentration-time curve from pre-dose (time 0) to the concentration on day 112
$AUC_{0\text{-}last}$	Area under the concentration-time curve from pre-dose (time 0) to the last quantifiable concentration
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinite time [redacted]
$t_{½}$	Terminal elimination half life
λ_Z	First-order terminal elimination rate constant [redacted]
	[redacted]
CL	Clearance [redacted]
V_d	Volume of distribution [redacted]

4.1.5.1 Pharmacokinetic Parameter Calculation Methods

[redacted]

- [redacted]
- [redacted]
- [redacted].

PK parameters will be estimated according to the following guidelines:

- C_{max} will be obtained directly from the concentration-time data.
- t_{max} is the actual time at which C_{max} is observed.
- λ_Z will be estimated at terminal phase [redacted]

- [redacted]
- [redacted]

4.1.6 Pharmacodynamic (PD) Variables

Blood samples for PD parameters will be drawn in accordance with the Schedule of Assessments in Table 1.

Change from baseline will be calculated for each of following PD parameters:

- Immunoglobulin levels (total serum IgA, IgG and IgM)
- lymphocytes (and their subsets) for cohort 1-4
- Immunoglobulin subtypes (IgA and IgG), [redacted]
- [redacted]

Table 5 Immune Assessment B Cell Subsets, B

[redacted]
[redacted]
Immune Assessment B Cell Subsets, B
[redacted]

[redacted]

Table 6 Immunoglobulin Subtypes

IgA subtypes: [redacted]
IgG subtypes: [redacted]

And also time to recovery of total serum IgA, IgG and IgM will be analyzed, two measures will be used:

1) Time to return to normal range (for those parameters that fall below LLN).

[redacted]

4.1.7 Anti-drug Antibody (ADA) Response

The serum samples for ADA of VIS649 will be collected at the time points detailed in the Schedule of Assessments in Table 1, and the data of ADA and titers will be analyzed.

4.1.8 Assessment of Response to Tetanus and Diphtheria Vaccination

Data of assessment of response to tetanus/diphtheria vaccination will be collected by subject for cohort 5 only at the time points detailed in the Schedule of Assessments in Table 1.

4.2 Analysis Populations

4.2.1 Safety population

All randomized subjects who received at least one dose of study drug. Subjects will be included in the analysis according to the dose and study drug received.

4.2.2 Pharmacokinetic (PK) population

All randomized subjects with at least one quantifiable VIS649 concentration. Subjects will be included in the analysis according to the dose and study drug received.

4.2.3 Pharmacodynamic (PD) population

The safety population subset with at least one PD parameter assessment (IgA, IgG, IgM) post study drug (VIS649 or placebo) dosing. Subjects will be included in the analysis according to the dose and study drug received.

4.3 Statistical Analysis Methods

4.3.1 Listings and Descriptive Statistics

All original and derived parameters will be listed. Listings will be by cohort, dose, subject and, where applicable, time post dose.

All listings will include repeated and unscheduled measurements.

The following rules will apply to any repeated measurements:

- If the repeated measurement occurs prior to the first dose of study drug, then the last obtained value of any repeated measurement will be used in the descriptive statistics.
- If the repeated measurement occurs after the first dose of study drug, then the original value of any repeated measurements will be used in the descriptive statistics.

Frequency counts (number of subjects [n] and percentages) will be presented for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated and presented for each quantitative variable (unless otherwise stated).

The rules with regards to the presentation of the frequency counts (number of subjects [n] and percentages) are as follows: if frequency count is 0, percentage will not be presented; if percentage is 100%, no decimal places will be given.

All descriptive statistics will be presented by treatment (dose). Subjects who receives placebo within cohort 1 - 4 will be presented as pooled placebo group, and subjects receiving placebo within cohort 5 will be used as individual placebo group as well. Data grouped from cohort 1-4, cohort 5 only and overall (all cohorts) may be analysed separately. In addition, a pooled VIS649 group (i.e. all subjects who receive VIS649 regardless of dose) will be presented for demographics, disposition, and adverse event. The baseline for all measurements (where applicable) will be the last pre-dose measurement unless specified.

4.3.1.1 Rounding Conventions for Safety Data

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of safety data:

- All data will be listed according to the number of decimal places presented in the source data.
- Mean and median will be tabulated to one more decimal place than the source data.
- Minimum and maximum values will be tabulated to the same number of decimal places as the source data.
- Standard deviation (SD) will be tabulated to two more decimal places than the source data.
- Coefficient of variation (CV)%, if applicable, will be presented to one decimal place.
- A maximum of three decimal places will apply to all summary statistics.

4.3.1.2 Rounding Conventions for Pharmacokinetic Data

PK Concentration Data:

The following rules will be followed with regards to the number of decimal places and presentation of data in tables and listings of concentration data:

- Source PK concentrations data shall be displayed in µg/mL without prior rounding

- The mean, standard deviation (SD), geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of three significant digits.
- Geometric coefficient of variation (CV) % and coefficient of variation (CV%) will be presented to one decimal place.

PK Parameter Data:

The following rules will be followed with regards to the number of decimal places and presentation of data in tables and listings of concentration data:

Individual PK Parameters	**$AUC_{0\text{-}112d}$ $AUC_{0\text{-}last}$ $AUC_{0\text{-}inf}$**	**C_{max}**	**T_{max}**	**λ_z**	**$t_{1/2}$**	**CL**	**V_d**
Decimal place for listing	0	2	2	4	1	2	0
Unit	h*ug/mL	ug/mL	h	1/h	h	mL/h	mL

- The mean, geometric mean, median and SD values will be reported to four significant digits, all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place.
- For tmax the minimum and maximum will be presented to two decimals places and all other descriptive statistics will be presented to three decimal places.
- Summary statistics will be calculated from unrounded estimates.

4.3.2 Statistical Significance Level

All statistical tests will be performed at the 5% level of significance and confidence intervals (CI) will be two-sided at the stated coverage probability.

4.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.2 or later. The PK analysis will be performed using WinNonlin Professional Software Version 8.0 or later.

4.3.4 Missing Data

There will be no imputation of missing data done except for defining Treatment Emergent Adverse Event (TEAE) and for defining prior and concomitant classification.

4.3.4.1 Imputation of Partial Start Dates and Times in defining TEAE data:

Any AEs with incomplete start dates/times will be handled according the following rules for classification as treatment-emergent respectively. Such imputations will only be performed for these classifications:

- Adverse events with completely unknown start dates will be imputed with the date of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening. Any AEs begin or worsen in severity on Day 1 are TEAEs.
- Adverse events with partially known start dates/times will be treated as follows:
    - Adverse events with unknown start times (but where the date is known) and where the start date is different to the dosing date, will be imputed with a time of 00:00 h for calculations. If the start date is the same as the dosing date the start time will be imputed to the dose time, so the AE is reported as treatment emergent.
    - If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which the study drug was administered, then the day will be imputed with the first day on which the study drug was administered in that month. If this results in a start date after the end date then the day will be imputed with the first day of the month.
    - If only the month is missing and the year is a year in which the study drug was administered, then the month will be imputed with the first month in which the study

drug was administered. If this results in a start date after the end date of the AE then the month will be imputed with JAN. If the known year part is not a year in which the study drug was administered then the month will also be imputed with JAN.

- If both the day and month is missing and the year is a year in which the study drug was administered then the day and month will be imputed with the day and month of dosing. If this results in a start date after end date then the day and month will be imputed with 01JAN. If the year is not a year in which the study drug was administered then the day and month will also be imputed with 01JAN.
- If only the year is missing then the year will be imputed with the year of dosing.

4.3.4.2 Handling Missing Severity and Causality Data of AEs

- Handling of unknown severity grades:
  - If the severity of an AE is missing, the severity will be designated as "severe" for analysis purposes.
- Handling of unknown causality assessment data:
  - If the causality of an AE is missing, the causality of the AE will be designated as "related" for analysis purposes.

4.3.4.3 Prior and Concomitant Medications

For prior and concomitant medication, there will be no imputation of missing data. If missing data prevents the medication being classified as prior or concomitant, the medication will be considered as concomitant for the data listings.

4.3.5 Interim Analysis

As participants in each dosing group complete their Week 16 visit, data clean-up and soft-lock will be performed for each cohort, in order to allow an interim assessment of PK, PD and safety data. PK/PD analysts will be permitted access to unblinded data, and to facilitate preparation of blinded data summaries for presentation to the Sponsor. The randomization code will be provided to the bioanalytical laboratories responsible for the analysis PK and PD endpoints. Following analysis of the

samples but prior to provision of the data to PAREXEL's statistician, the laboratory will re-code the data back to the corresponding original unique sample ID numbers, enabling differentiation but not identification of the subjects in order to maintain blinding integrity for the other assessments of the clinical study, until after database lock. The full randomization code will be broken only for purposes of data analysis and reporting or safety reasons. This will occur once all final data have been entered into the database and all data queries have been resolved, coding is complete, the assignment of subjects to the analysis sets has been completed and the database has been locked.

Interim summaries of PK, PD and safety data for selected or entire cohorts (inclusive of both VIS649 and placebo recipients, and therefore, still blinded) may be utilized for various reporting purposes prior to full database lock and unblinding if deemed appropriate.

4.3.6 Subject Information

4.3.6.1 Randomization Scheme and Codes

Each subject has their unique enrollment (subject) number and randomization number. The randomization number will be used as subject identification in TLFs.

4.3.6.2 Subject Disposition

The completion status and the reason for discontinuation of subjects using the randomized population will be listed [Listing 16.2.1.1] and summarized [Table 14.1.1]. The number and percentage of subjects entering and completing each treatment of the clinical study will be presented, including the number and percentage of subjects dosed, the frequency and percentage of subjects completing the treatment, and the frequency and percentage of subjects completing the study,, subjects withdrawing early, and primary reason for withdrawal will be included the summary table.

Listing of the informed consent will be presented using the randomized population [Listing 16.2.1.2].

Subjects who did not meet the inclusion criteria will be listed [Listing 16.2.1.3], and subjects who did meet the exclusion criteria will be listed [Listing 16.2.1.4].

Subject visits information will be listed using the safety population [Listing 16.2.1.5].

4.3.6.3 Protocol Deviations

All protocol deviations will be recorded by the Investigator and will be listed by subject and will be discussed between PAREXEL (physician, Data Manager, Biostatistician, PK Scientist/Analyst and Medical Writer) and the Sponsor during the clean file meeting before database lock to determine whether these may warrant exclusion of a subject from the statistical analyses. All protocol deviations will be listed for each subject [Listing 16.2.2].

4.3.6.4 Analysis Population

Classification to analysis populations will be presented in a listing and table [Listing 16.2.3, Table 14.1.2].

4.3.6.5 Demographic and Baseline Data

All demographic and baseline data, including height, weight and BMI, will be presented using the safety population. All demographic and baseline data including height, weight and BMI will be listed [Listing 16.2.4.1]. Descriptive statistics will be obtained for the continuous variables by dose and by ethnicity: age, height, Day -1 weight, and BMI [Tables 14.1.3.1 and 14.1.3.2 respectively]. Frequencies and percentages of subjects will be tabulated for the categorical variables by dose and by ethnicity: gender, race, and ethnicity [Tables 14.1.3.3 and 14.1.3.4 respectively].

All other baseline characteristics, including drug abuse, alcohol abuse, smoking history, caffeine use, other stimulating beverages, and blood or plasma donation will be listed [Listing 16.2.4.2].

Detailed information of tobacco product use will be listed [Listing 16.2.4.3].

Detailed information of alcohol use will be listed [Listing 16.2.4.4].

4.3.6.6 Medical History

All medical history will be coded using MedDRA version 21.1.

General medical history and medication history will be listed by subject [Listing 16.2.4.5], including the disease/procedure, MedDRA System Organ Class (SOC), MedDRA Preferred Term (PT), start date, and stop date (or ongoing if applicable). Only those body systems where a condition or abnormality has been reported will be listed.

Reproductive history (female only) will be listed [Listing 16.2.4.6].

4.3.6.7 Laboratory Tests at Screening and Check-in

Laboratory tests performed at screening and check-in (serology, drug and alcohol toxicology screen tests) will be listed using the safety population [Listing 16.2.4.7].

Pregnancy test performed at screening and check-in (serum and urine tests) will be listed using female subjects only in the safety population [Listing 16.2.4.8].

4.3.6.8 Prior and Concomitant Medication

Prior and concomitant medication will be listed by subject using the safety population [Listing 16.2.4.9], the listing will include the following information: reported name, preferred term, the route of administration, dose, frequency, start date/time, duration and indication.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO Drug Version Global September 2018 B3).

4.3.6.9 Exposure to the Investigational Medicinal Product

The administration of the study drug VIS649 or placebo for the safety population will be listed with dose amounts and times [Listing 16.2.5.1]. Study drug compliance will be summarized [Table 14.1.4].

Tetanus/Diphtheria vaccination of subjects in cohort 5 will be listed with dose amounts and Date time [Listing 16.2.5.2].

4.3.7 Pharmacokinetic Concentration and Parameter Analyses

The analysis of the PK data will be based on the PK population.

For cohort 5, if number of either Japanese subjects or non-Japanese subjects is less than 3, cohort 5 won't be included in "by ethnicity" analysis.

Pharmacokinetic Concentrations

Pharmacokinetic VIS649 serum concentration data will be listed by subject, including actual sampling times relative to dosing and the deviation from the scheduled sampling time [Listing 16.2.6.1].

Concentrations will be summarized by dose and nominal PK sampling time [Table 14.2.1].
Concentrations will be summarized by ethnicity, dose and nominal PK sampling time [Table 14.2.2].

The following descriptive statistics will be used: n, arithmetic mean, geometric mean, SD, coefficients of variation (CV%), geometric CV% [redacted], minimum, maximum and median. The number of values above the lower limit of quantification (LLOQ) will also be presented.

Handling of values below the limit of quantification (BLQ) in listings and for the calculation of descriptive statistics at each time point:

All concentrations below the limit of quantification (BLQ) or missing data will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NS") and excluded from analysis. Values that are BLQ will be substituted with zero for the calculation of descriptive statistics of concentration by time point and will be displayed as “not calculable” or NC for the calculation of statistical summaries.

- Figure 14.2.1.1: Combined Subject Profiles for VIS649 Plasma Concentration Time Data-Linear Scale
- Figure 14.2.1.2: Combined Subject Profiles for VIS649 Plasma Concentration Time Data - Semi-Logarithmic Scale

  The actual sampling time will be used on the x-axis. Time on the x-axis will be in days.
- Figure 14.2.1.3: Mean (± SD) Plasma VIS649 Concentration Time Data -Linear Scale
- Figure 14.2.1.4: Mean Plasma VIS649 Concentration Time Data - Semi-Logarithmic Scale

  The nominal sampling time will be used on the x-axis. All treatments will be overlaid on the same plot. Time on the x-axis will be in days.

To visualize the comparison between ethnicity groups for each treatment the following descriptive pharmacokinetic graphs will be generated. For each figure Japanese and Non-Japanese subjects will be shown on the same plot with separate figures for each level of treatment. Figures will be displayed in black and white.

- Figure 14.2.1.5: Japanese vs Non-Japanese Mean (± SD) Plasma VIS649 Concentration Time Data -Linear Scale
- Figure 14.2.1.6: Japanese vs Non-Japanese Mean Plasma VIS649 Concentration Time Data - Semi-Logarithmic Scale - The nominal sampling time will be used on the x-axis. All treatments will be overlaid on the same plot. Time on the x-axis will be in days

Pharmacokinetic Parameters

Pharmacokinetic parameters will be listed [Listing 16.2.6.2] and summarized by dose [Table 14.2.3] and by ethnicity and dose [Table 14.2.4] separately.

The summaries of PK parameters will use following descriptive statistics: n, arithmetic means, SD, coefficients of variation (CV%), geometric CV% [redacted], minimum, maximum and median. For t_{max} only median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

No value for $AUC_{0\text{-inf}}$, CL, $t_{1/2}$, or Vd, will be reported for cases with inaccurate estimation of λ_z.

Dose Proportionality Analysis

Due to the complex nature of the association between the systemic exposure and the dose, the assessment of the dose proportionality will not be based solely on a strict statistical rule given the small sample size for each dose level. Rather, several considerations will be taken into account for assessing dose proportionality, such as results derived from the Power Model (e.g., the slope estimate, and the width of the 95% confidence intervals) and qualitative assessment specific to the PK of the drug and clinical relevance.

[redacted]

[redacted]

Table 14.2.5.1 will summarize the results of the regression analysis.

To assess the linear relationship with the dose of VIS649 administered graphically, scatter plots of serum PK parameters (dose normalized to a 1mg dose) versus dose will be generated for the dose dependent PK parameters C_{max}, AUC $_{0\text{-}112d}$, AUC $_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ (Figure 14.2.1.7), the figure will include the 90% CI prediction and confidence band.

Ethnicity Effect on PK

[redacted]

RUN;

QUIT;

Table 14.2.5.2 will present ANCOVA results for pharmacokinetic parameters by dose and will have least square estimate and 95 % CI for the geometric means for each ethnicity along with the 90% CI for the ratio of geometric means (test=Japanese / reference=non-Japanese).

4.3.8 Pharmacodynamic Variables

The analysis of the PD data will be based on the PD population.

For cohort 5, if number of either Japanese subjects or non-Japanese subjects is less than 3, cohort 5 won't be included in "by ethnicity" analysis.

As secondary endpoints, individual subject pharmacodynamics data of serum concentrations of Immunoglobulin levels (total IgA, IgG and IgM) will be listed [Listings 16.2.6.3.1 (observed) and 16.2.6.3.2 (change from baseline)], observed and change from baseline will be summarized descriptively by treatment [Tables 14.2.7.1 (Immunoglobulin)] and by ethnicity and treatment [Tables 14.2.7.2 (Immunoglobulin)].

Individual subject circulating lymphocytes and lymphocyte subsets will be listed [Listings 16.2.6.4.1 (observed) and 16.2.6.4.2 (change from baseline), and 16.2.6.5.1 (observed) and 16.2.6.5.2 (change from baseline) respectively]; observed values and change from baseline will be summarized descriptively by treatment [Tables 14.2.8.1 (lymphocytes), and 14.2.9.1 (lymphocyte subsets), separately] and by ethnicity and treatment [Tables 14.2.8.2 (lymphocytes), and 14.2.9.2 (lymphocyte subsets), separately]. This assessment will be done for all lymphocytes, and also for lymphocyte subsets that are noted to show changes from baseline. These analyses will be conducted for cohorts 1-4 only.

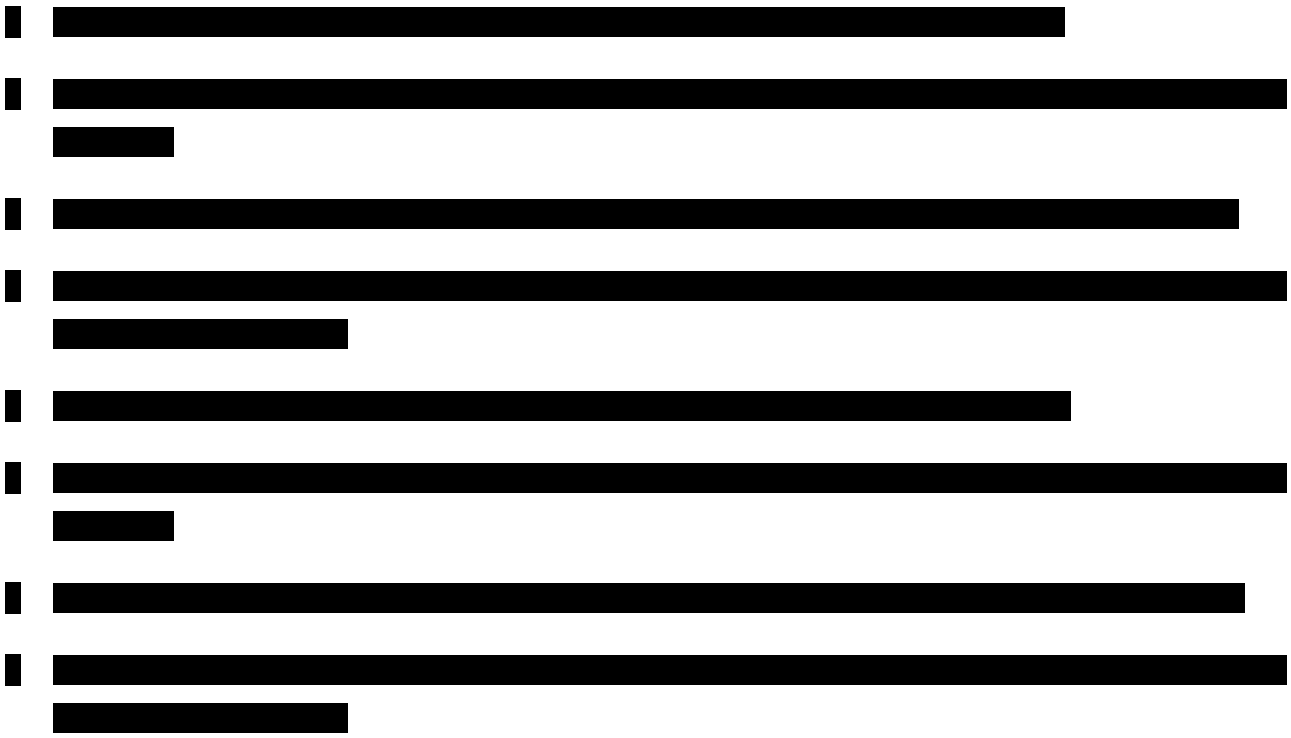
Individual observed value, change from baseline and percent change from baseline plots against time (Figures [Total IgA: 14.2.2.1.1, 14.2.2.1.2 and 14.2.2.1.3], [Total IgG: 14.2.2.2.1, 14.2.2.2.2, and 14.2.2.2.3], [Total IgM: 14.2.2.3.1, 14.2.2.3.2 and 14.2.2.3.3]), and individual observed value, change from baseline plots against time (Figures [Lymphocytes (cohorts 1-4 only): 14.2.2.4.1 and 14.2.2.4.2], and [Lymphocyte subsets (cohorts 1-4 only): 14.2.2.5.1 and 14.2.2.5.2]) will be produced by treatment with each subject being identifiable. The actual sampling time will be used in days on the x-axis.

Mean (±SD), mean change from baseline and percent mean change from baseline plots against time (Figures [Total IgA: 14.2.2.1.4, 14.2.2.1.5 and 14.2.2.1.6], [Total IgG: 14.2.2.2.4, 14.2.2.2.5 and

14.2.2.2.6], [Total IgM: 14.2.2.3.4, 14.2.2.3.5 and 14.2.2.3.6]), and mean (±SD) and change from baseline plots against time (Figures [Lymphocytes (cohorts 1-4 only): 14.2.2.4.3 and 14.2.2.4.4] , and [Lymphocyte subsets (cohorts 1-4 only): 14.2.2.5.3 and 14.2.2.5.4]) will be presented by treatment; Mean(±SD), mean change from baseline and percent mean change from baseline plots against time by ethnicity and treatment (Figures [Total IgA: 14.2.2.1.7, 14.2.2.1.8 and 14.2.2.1.9], [Total IgG: 14.2.2.2.7, 14.2.2.2.8 and 14.2.2.2.9], [Total IgM: 14.2.2.3.7, 14.2.2.3.8 and 14.2.2.3.9]), and mean(±SD) and change from baseline plots against time by ethnicity and treatment (Figures [Lymphocytes(cohorts 1-4 only): 14.2.2.4.5 and 14.2.2.4.6] , and [Lymphocyte subsets (cohorts 1-4 only): 14.2.2.5.5 and 14.2.2.5.6]) will be presented as well. The nominal sampling time will be used in days on the x-axis. All treatments will be overlaid on the same plot. [redacted]

Following figures will be created:

- Figure 14.2.2.6.1: IgA subtype mean (±SD) over time by treatment
- Figure 14.2.2.6.2: IgA subtype mean (±SD) change from baseline over time by treatment
- Figure 14.2.2.6.3: IgA subtype mean (±SD) over time by ethnicity and treatment
- Figure 14.2.2.6.4: IgA subtype mean (±SD) change from baseline over time by ethnicity and treatment
- Figure 14.2.2.7.1: IgG subtype mean (±SD) over time by treatment
- Figure 14.2.2.7.2: IgG subtype mean (±SD) change from baseline over time by treatment
- Figure 14.2.2.7.3: IgG subtype mean (±SD) over time by ethnicity and treatment
- Figure 14.2.2.7.4: IgG subtype mean (±SD) change from baseline over time by ethnicity and treatment



If a baseline PD value is zero, then the percentage change from baseline will not be calculated. If a PD value is BLQ then the value will be set to the LLOQ. Similarly, for the PD plots, a BLQ value will be set equal to LLOQ.

4.3.9 Pharmacokinetic/Pharmacodynamic Analysis

An exploratory PK/PD analysis between the serum concentrations of the study drug and PD assessments may be performed, if deemed appropriate. These exploratory methods may include PK/PD modeling to describe the impact of drug concentration on the inhibition of immunoglobulin production. The decision to perform this analysis will be made by the Sponsor and may require a SAP addendum.

4.3.10 Anti-drug Antibody (ADA) Response Analysis

For cohort 5, if number of either Japanese subjects or non-Japanese subjects is less than 3, cohort 5 won't be included in "by ethnicity" analysis.

Anti-VIS649 ADA evaluations will be listed including the confirmatory assay (positive/negative) and titers [Listing 16.2.10.1]. A "titre specific cut-point" might be used to assess titer, another category, for

these subjects that are confirmed positive based on the screening cut-point that are not considered positive for titer, might be included in the listing and be footnoted.

A summary table of the ADA response (positive or negative) will be presented, by treatment (cohort 1-4 or pooled placebo or cohort 5 or cohort 5 placebo) and by ethnicity and dose separately, based on the Safety Population [Tables 14.3.8.1 and 14.3.8.2]. In addition, the ADA titers (log10) (n, median, minimum and maximum) will be summarized by treatment (cohort 1-4 or pooled placebo or cohort 5 or cohort 5 placebo) and by ethnicity and treatment - separately for all subjects with a positive confirmatory assay at each time point [Tables 14.3.8.3 and 14.3.8.4], this tabulation will include a summary of the highest titer across all time points for each subject.

[redacted]

Following figures will be created for ADA titers.

- Figure 14.2.3.1: Spaghetti Plot of ADA log10 (titer) Over Time (Safety Population). For each dose separately, spaghetti plot of log10 (titer) vs. time, split in pre-Ab negative and pre-Ab positive population will be generated for subjects.
- Figure 14.2.3.2: Mean ADA log10 (titer) Over Time (Safety Population). For each dose separately, line plot of the mean log10 (titer) vs. time, split in pre-Ab negative and pre-Ab positive population will be generated for dose groups.

[redacted]

4.3.11 Safety Analysis

The analysis of the safety variables will be based on the Safety Population.

4.3.11.1 Adverse Events

The following listing and tables will be produced:

- All Pre-treatment and treatment-emergent AE [Listing 16.2.7].
- All Serious AEs (if applicable) [Listing14.3.2.1].
- All Adverse Events Leading to Discontinuation (if applicable) [Listing 14.3.2.2].

The following information will be included in the listings: Verbatim, system organ class (SOC), preferred term (PT), AE onset date (and time) and study day, AE end date (and time) and duration (days), severity, relationship to IMP, AE outcome, TEAE indicator flag and SAE indicator flag.

An overall summary of all treatment-emergent adverse events [Table 14.3.1.1] will present the number and percentage of subjects, as well as number of events, according to the following categories:

- All treatment emergent adverse events
- Emergent adverse events Related to IMP

- Mild treatment emergent adverse events
- Moderate treatment emergent adverse events
- Severe treatment emergent adverse events
- Serious treatment emergent adverse events
- Treatment emergent adverse events leading to early termination
- Deaths

Other summary tables for adverse events will include:

- Table 14.3.1.2: Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, and Preferred Term
- Table 14.3.1.3: Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity
- Table 14.3.1.4: Number and Percentage of Subjects with Treatment Emergent Adverse Events "Related to IMP" by System Organ Class, Preferred Term, and Severity
- Table 14.3.1.5: Number and Percentage of Subjects with Treatment Emergent Adverse Events "Not Related to IMP" by System Organ Class, Preferred Term, and Severity

If a subject has multiple AEs with the same preferred term but occurring after each dose administration, then one AE will be counted for each treatment.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, and then alphabetically for SOC, and PT within SOC.

4.3.11.2 Clinical Safety Laboratory Tests (biochemistry, hematology, coagulation, and urinalysis)

Laboratory values (biochemistry, hematology, coagulation, and urinalysis) will be listed [Listings 16.2.8.1, 16.2.8.2, 16.2.8.3, and 16.2.8.4 respectively]. The baseline for the laboratory values will be the results obtained on Day -1; if this is missing then the screening value or, if available, a pre-dose unscheduled measurement will be used (whichever is closer to the baseline date).

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

Individual results of laboratory tests from serum chemistry, hematology, coagulation, and urinalysis outside of the laboratory normal ranges will be listed by subject, laboratory group, test and time point [Listings 14.3.4.1, 14.3.4.2, 14.3.4.3, and 14.3.4.4 respectively].

Baseline and post-dose visit data will be summarized for all serum chemistry [Tables 14.3.5.1.1 (observed) and 14.3.5.1.2 (change from baseline)], hematology [Tables 14.3.5.2.1 (observed) and 14.3.5.2.2 (change from baseline)], coagulation [Tables 14.3.5.3.1 (observed) and 14.3.5.3.2 (change from baseline)], urinalysis [Tables 14.3.5.4.1 (observed) and 14.3.5.4.2 (change from baseline)]. Observed and change from baseline for quantitative data will be summarized. Descriptive summary statistics will include n (number of observations), mean, SD, median, minimum, maximum.

Laboratory shift tables from baseline to each post-dose visit will be presented for serum chemistry [Table 14.3.5.5], hematology [Table 14.3.5.6], coagulation [Table 14.3.5.7], and urinalysis [Table 14.3.5.8].

4.3.11.3 Vital Signs

Height, weight, BMI and Body temperature will be listed [Listing 16.2.9.1.1].

Blood pressure, heart rate and respiratory rate observed and change from baseline data will be listed [Listings 16.2.9.1.2 and 16.2.9.1.3 separately]. Baseline will be taken as the pre-dose assessment on Day 1; if this is missing then the screening value or, if available, a pre-dose unscheduled measurement will be used (whichever is closer to the baseline date).

Observed values and changes from baseline will be summarized [Tables 14.3.6.1 and 14.3.6.2].

4.3.11.4 Twelve-Lead Electrocardiogram

The individual data and investigators overall interpretation of the 12-lead ECG results and change from baseline will be listed [Listings 16.2.9.2.1 and 16.2.9.2.2 separately]. Baseline will be taken as the pre-dose assessment on Day 1; if this is missing then the screening value or, if available, a pre-dose unscheduled measurement will be used (whichever is closer to the baseline date).

Observed values and changes from baseline will be summarized [Table 14.3.7.1 and 14.3.7.2].

The incidence of abnormalities, based on the clinical interpretations from the investigator, will be counted by treatment and visit [Table 14.3.7.3].

4.3.11.5 Physical Examination

The abnormal results of the physical examination will be listed [Listing 16.2.9.3].

4.3.11.6 Response to Tetanus/Diphtheria Vaccination

Tetanus and diphtheria immunity are assessed by measurement of anti-tetanus and anti-diphtheria toxoid IgG serum levels, respectively, by neutralization assay or by.

For cohort 5, IgG data of Tetanus/diphtheria serology assessment will be listed [Listing 16.2.8.5]. Summary of observed and change from baseline for IgG will be tabulated [Tables 14.3.5.9]. Serum IgG level for tetanus and diphtheria following a dose of TENIVAC vaccine will be summarized separately by treatment, timepoints [Tables 14.3.5.10, 14.3.5.11]. Levels of serum IgG for tetanus: >0.1IU/mL and >1.0 IU/mL and levels of serum IgG for diphtheria: >0.01IU/mL, >0.1IU/mL and >1.0 IU/mL will be used for summary.

5. REFERENCES

1. SAS® Version 9.2 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 8.0. http://www.pharsight.com
3. Sanofi Pasteur 420 – TENIVAC Full Prescribing Information

6. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Subject Disposition

Table 14.1.1 Subject Disposition and Reasons for Discontinuation (Safety Population)

Table 14.1.2 Analysis population (Safety Population)

Baseline and Demographic Data

Table 14.1.3.1 Subject Demographics – Continuous Measures (Safety Population)

Table 14.1.3.2 Subject Demographics by Ethnicity – Continuous Measures (Safety Population)

Table 14.1.3.3 Subject Demographics – Categorical Measures (Safety Population)

Table 14.1.3.4 Subject Demographics by Ethnicity – Categorical Measures (Safety Population)

Table 14.1.4 Summary of Study Drug Compliance (Safety Population)

Pharmacokinetic Data

Table 14.2.1 VIS649 Serum Concentrations (unit) Over Time by Treatment (Pharmacokinetic Population)

Table 14.2.2 VIS649 Serum Concentrations (unit) Over Time by Ethnicity and Treatment (Pharmacokinetic Population)

Table 14.2.3 Summary of Pharmacokinetic Parameters of VIS649 by Treatment (Pharmacokinetic Population)

Table 14.2.4 Summary of Pharmacokinetic Parameters of VIS649 by Ethnicity and Treatment (Pharmacokinetic Population)

Table 14.2.5.1 Statistical Analysis of Dose Proportionality of VIS649 Pharmacokinetic Parameters (Pharmacokinetic Population)

Table 14.2.5.2 Statistical Assessment of Ethnicity Effect on VIS649 Pharmacokinetic

Parameters (Pharmacokinetic Population)

Table 14.2.6.1.1 VIS649 Serum Concentrations Descriptive Statistics by Overall Subject ADA Classification by Treatment (Pharmacokinetic Population)

Table 14.2.6.1.2 VIS649 Serum Concentrations Descriptive Statistics by Overall Subject ADA Classification by Treatment and Ethnicity (Pharmacokinetic Population)

Table 14.2.6.2.1 Pharmacokinetic Parameters of VIS649 Descriptive Statistics by Overall Subject ADA Classification by Treatment (Pharmacokinetic Population)

Table 14.2.6.2.2 Pharmacokinetic Parameters of VIS649 Descriptive Statistics by Overall Subject ADA Classification by Treatment and Ethnicity (Pharmacokinetic Population)

Pharmacodynamic Data

Table 14.2.7.1 Summary of Pharmacodynamic Parameters by Treatment : Immunoglobulin (Pharmacodynamic Population)

Table 14.2.7.2 Summary of Pharmacodynamic Parameters by Ethnicity and Treatment : Immunoglobulin (Pharmacodynamic Population)

Table 14.2.7.3 Summary of Pharmacodynamic Parameters by Treatment : Immunoglobulin Subtypes (Pharmacodynamic Population)

Table 14.2.7.4 Summary of Pharmacodynamic Parameters by Ethnicity and Treatment : Immunoglobulin Subtypes (Pharmacodynamic Population)

Table 14.2.7.5 Summary of Pharmacodynamic Parameter by Treatment: APRIL (Pharmacodynamic Population)

Table 14.2.7.6 Summary of Pharmacodynamic Parameter by Ethnicity and Treatment: APRIL (Pharmacodynamic Population)

Table 14.2.7.7 Summary of Pharmacodynamic Parameter by Treatment: a-g IgA (Pharmacodynamic Population)

Table 14.2.7.8 Summary of Pharmacodynamic Parameter by Ethnicity and Treatment: a-g IgA (Pharmacodynamic Population)

Table 14.2.8.1 Summary of Pharmacodynamic Parameters by Treatment : Lymphocytes (Pharmacodynamic Population)

Table 14.2.8.2 Summary of Pharmacodynamic Parameters by Ethnicity and Treatment : Lymphocytes (Pharmacodynamic Population)

Table 14.2.9.1 Summary of Pharmacodynamic Parameters by Treatment : Lymphocyte Subsets (Pharmacodynamic Population)

Table 14.2.9.2 Summary of Pharmacodynamic Parameters by Ethnicity and Treatment : Lymphocyte Subsets (Pharmacodynamic Population)

Safety Data

Adverse Events

Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events (Safety Population)

Table 14.3.1.2 Treatment-Emergent Adverse Events by Treatment, System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.3 Treatment-Emergent Adverse Events by Treatment, System Organ Class, Preferred Term and Maximum Severity (Safety Population)

Table 14.3.1.4 Treatment Emergent Adverse Events "Related to IMP" by System Organ Class, Preferred Term and Severity (Safety Population)

Table 14.3.1.5 Treatment Emergent Adverse Events "Not Related to IMP" by System Organ Class, Preferred Term and Severity (Safety Population)

Listing 14.3.2.1 All Serious Adverse Events (Safety Population)

Listing 14.3.2.2 Adverse Events Leading to Discontinuation (Safety Population)

Clinical Laboratory Tests

Table 14.3.8.4 Summary of Anti-VIS649 ADA Titer (log10) by Ethnicity and Treatment (Safety Population)

7. FIGURES

Pharmacokinetic Data

Figure 14.2.1.1 Combined Subject Profiles for Plasma VIS649 Concentration Time Data - Linear Scale (Pharmacokinetic Population)

Note: One page per dose, spaghetti plots. The x-axis [may extend to 112 days or may] will be truncated to represent the period of quantifiable data. Add BLQ footnote

Figure 14.2.1.2 Combined Subject Profiles for Plasma VIS649 Concentration Time Data - Semi-Logarithmic Scale (Pharmacokinetic Population)

Note: One page per dose/ethnicity, spaghetti plots. The x-axis [may extend to 112 days or may] will be truncated to represent the period of quantifiable data. Add BLQ footnote

Figure 14.2.1.3 Mean (± SD) Plasma VIS649 Concentration Time Data - Linear Scale (Pharmacokinetic Population)

Note: One page per dose overlay. Plot mean (+/- SD) with different symbols by treatment. X-axis in common with previous figures. Add BLQ footnote.

Figure 14.2.1.4 Mean Plasma VIS649 Concentration Time Data - Semi-logarithmic Scale (Pharmacokinetic Population)

Note: One page per dose overlay. Plot mean with different symbols by treatment. X-axis in common with previous figures. Add BLQ footnote.

Figure 14.2.1.5 Japanese vs Non-Japanese Mean (± SD) Plasma VIS649 Concentration Time Data - Linear Scale (Pharmacokinetic Population)

Note: The nominal sampling time will be used on the x-axis. All treatments will be overlaid on the same plot. Time on the x-axis will be in days.

Figure 14.2.1.6 Japanese vs Non-Japanese Mean Plasma VIS649 Concentration Time Data -

Semi-Logarithmic Scale (Pharmacokinetic Population)

Note: The nominal sampling time will be used on the x-axis. All treatments will be overlaid on the same plot. Time on the x-axis will be in days

Figure 14.2.1.7 Dose Proportionality of VIS649 Pharmacokinetic Parameters (Pharmacokinetic Population)

Pharmacodynamic Data

Figure 14.2.2.1.1 Individual IgA over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.2 Individual IgA Change from Baseline over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.3 Individual IgA Percent Change from Baseline over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.4 IgA Mean (±SD) over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.5 IgA Mean (±SD) Change from Baseline over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.6 IgA Percent Mean (±SD) Change from Baseline over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.7 IgA Mean (±SD) over Time by Ethnicity and Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.8 IgA Mean (±SD) Change from Baseline over Time by Ethnicity and Treatment (Pharmacodynamic Population)

Figure 14.2.2.1.9 IgA Percent Mean (±SD) Change from Baseline over Time by Ethnicity and Treatment (Pharmacodynamic Population)

Figure 14.2.2.2.1 Individual IgG over Time by Treatment (Pharmacodynamic Population)

Figure 14.2.2.2.2 Individual IgG Change from Baseline over Time by Treatment

Figure 14.2.2.8.3 Mean (±SD) Change from Baseline of APRIL Concentration vs Time Data by Treatment - Linear Scale (Pharmacodynamic Population)

Figure 14.2.2.8.4 Mean (±SD) Change from Baseline of APRIL Concentration vs Time Data by Ethnicity and Treatment - Linear Scale (Pharmacodynamic Population)

Figure 14.2.2.9.1 Mean (±SD) a-g IgA Concentration vs Time Data by Treatment - Linear Scale (Pharmacodynamic Population)

Figure 14.2.2.9.2 Mean (±SD) a-g IgA Concentration vs Time Data by Ethnicity and Treatment - Linear Scale (Pharmacodynamic Population)

Figure 14.2.2.9.3 Mean (±SD) Change from Baseline of a-g IgA Concentration vs Time Data by Treatment - Linear Scale (Pharmacodynamic Population)

Figure 14.2.2.9.4 Mean (±SD) Change from Baseline of a-g IgA Concentration vs Time Data by Ethnicity and Treatment - Linear Scale (Pharmacodynamic Population)

Immunogenicity Data

Figure 14.2.3.1 Spaghetti Plot of ADA log10 (titer) over Time (Safety Population).

For each dose separately, For each dose separately, spaghetti plot of log10 (titer) vs. time, split in pre-Ab negative and pre-Ab positive population will be generated for subjects.

Figure 14.2.3.2 Mean ADA log10 (titer) over Time (Safety Population).

For each dose separately, line plot of the mean log10 (titer) vs. time, split in pre-Ab negative and pre-Ab positive population will be generated for dose groups.

Figure 14.2.3.3 Scatterplot of Pharmacokinetic Concentrations by Overall Subject ADA Classification (Pharmacokinetic Population)

Figure 14.2.3.4 Scatterplot of Pharmacokinetic Parameters by Overall Subject ADA Classification (Pharmacokinetic Population)

8. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

Subject Disposition

Listing 16.2.1.1 Subject Disposition (All Randomized Subjects)

Listing 16.2.1.2 Informed Consent (All Randomized Subjects)

Listing 16.2.1.3 Subjects Who Did Not Meet The Inclusion Criteria

Listing 16.2.1.4 Subjects Who Did Meet The Exclusion Criteria

Listing 16.2.1.5 Subject Visits (Safety Population)

Listing 16.2.2 Protocol Deviations

Listing 16.2.3 Assignment to Analysis Populations (Safety Population)

Baseline and Demographic Data

Listing 16.2.4.1 Subject Demographics (Safety Population)

Listing 16.2.4.2 Baseline Characteristics (Safety Population)

Listing 16.2.4.3 Tobacco Product Use (Safety Population)

Listing 16.2.4.4 Alcohol Use (Safety Population)

Listing 16.2.4.5 Medical History (Safety Population)

Listing 16.2.4.6 Reproductive History (Female Subject Only)

Listing 16.2.4.7 Laboratory Tests Performed at Screening and Check-in (Safety Population)
Note: Serology, drug and alcohol toxicology screening tests

Listing 16.2.4.8 Pregnancy Screening Tests (Female Subjects Only)

Concomitant Medication

Listing 16.2.4.9 Prior and Concomitant Medications (Safety Population)

Exposure

Listing 16.2.5.1 Study Drug Administration (Safety Population)

Listing 16.2.5.2 Tetanus/Diphtheria Vaccination (Safety Population Cohort 5 only)

Note: Tetanus/Diphtheria vaccine: TENIVAC® vaccine.

Pharmacokinetic Data

Listing 16.2.6.1 Blood Sampling Times and VIS649 Serum Concentrations (Safety Population)

Listing 16.2.6.2 Pharmacokinetic Parameters of VIS649 (Pharmacokinetic Population)

Pharmacodynamic Data

Listing 16.2.6.3.1 Individual Pharmacodynamic Blood Sampling Times and Concentrations of Immunoglobulin: Observed Value (Pharmacodynamic Population)

Listing 16.2.6.3.2 Individual Pharmacodynamic Blood Sampling Times and Concentrations of Immunoglobulin: Change from Baseline (Pharmacodynamic Population)

Listing 16.2.6.4.1 Individual Pharmacodynamic Blood Sampling Times and Lymphocyte Population: Observed Value (Pharmacodynamic Population)

Listing 16.2.6.4.2 Individual Pharmacodynamic Blood Sampling Times and Lymphocyte Population: Change from Baseline (Pharmacodynamic Population)

Listing 16.2.6.5.1 Individual Pharmacodynamic Blood Sampling Times and Lymphocyte Subsets: Observed Value (Pharmacodynamic Population)

Listing 16.2.6.5.2 Individual Pharmacodynamic Blood Sampling Times and Lymphocyte Subsets: Change from Baseline (Pharmacodynamic Population)

[redacted]

Safety Data

Adverse Events

Listing 16.2.7 All Adverse Events (Safety Population)

Clinical Laboratory Tests

Listing 16.2.8.1 Clinical Laboratory Data: Serum Chemistry (Safety Population)

Listing 16.2.8.2 Clinical Laboratory Data: Hematology (Safety Population)

Listing 16.2.8.3 Clinical Laboratory Data: Coagulation (Safety Population)

Listing 16.2.8.4 Clinical Laboratory Data: Urinalysis (Safety Population)

Listing 16.2.8.5 Tetanus/Diphtheria Serology (Safety Population Cohort 5 only)

Vital Sign

Listing 16.2.9.1.1 Vital Signs – Height, Weight, BMI and Body Temperature (Safety Population)

Listing 16.2.9.1.2 Vital Signs – Observed Values of Blood Pressure, Heart Rate and Respiratory Rate (Safety Population)

Listing 16.2.9.1.3 Vital Signs – Change from Baseline of Blood Pressure, Heart Rate and Respiratory Rate (Safety Population)

ECG

Listing 16.2.9.2.1 12-Lead Electrocardiogram: Observed Values (Safety Population)

Listing 16.2.9.2.2 12-Lead Electrocardiogram: Change from Baseline (Safety Population)

Physical Examination

Listing 16.2.9.3 Physical Examination Abnormal Findings (Safety Population)

Immunogenicity

Listing 16.2.10.1 Immunogenicity: ADA (Safety Population)

[redacted]

[redacted]