Clinical Study Protocol

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

Sponsor:	Visterra Inc. 275 2nd Avenue Waltham, MA 02451
Contract Research Organization:	PAREXEL International Early Phase Clinical Unit–Los Angeles 1560 Chevy Chase Drive, Suite 140 Glendale, CA 91206 USA
[redacted]	[redacted]
Sponsor Study Number:	VIS649-101
[redacted]	[redacted]
IMP Name:	VIS649
Development Phase:	Phase 1 safety and pharmacokinetics
Version (Date) of Final Protocol:	Final (20 AUG 2018)

This clinical study will be conducted in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (GCP) (E6), the protocol and with other applicable regulatory requirements.

Confidentiality Statement

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Expert

Protocol Title: 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

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product (IMP), as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: 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

This clinical study protocol was subjected to critical review and has been released by the Sponsor. The information it contains is consistent with current risk and benefit evaluation of the IMP, as well as with the moral, ethical and scientific principles governing clinical research as set out in the guidelines on GCP applicable to this clinical study.

Principal Investigator

[redacted]

LIST OF STUDY STAFF

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PROTOCOL SYNOPSIS

Protocol Title	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
Study Numbers	[redacted] Sponsor Protocol No.: VIS649-101
Development Phase	Phase 1, safety and pharmacokinetics (PK)
Sponsor	Visterra Inc.
Principal Investigator	[redacted]
Study Center	PAREXEL Early Phase Clinical Unit–Los Angeles
Study Objectives	**Primary Objective:** To evaluate the safety and tolerability of VIS649 in healthy subjects **Secondary Objectives:** • To characterize the PK profile of VIS649 • To evaluate the effect of race on the pharmacokinetic 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: o changes in serum total IgA, IgG and IgM concentrations and time to recovery o changes in whole blood circulating lymphocyte populations [redacted]
Study Design	This is a phase 1, randomized, placebo-controlled, double-blind, single ascending dose study of IV VIS649 in healthy subjects. Potential subjects will be carefully screened for eligibility prior to study enrollment. Randomization and blinding will occur according to a core randomization list administered by the site's unblinded pharmacist. The study will enroll up to 45 subjects and will be conducted in four sequential dosing cohorts at four different dose levels (0.5, 2.0, 6.0 and 12 mg/kg), enrolling 9 subjects per cohort. Subjects will be randomized to VIS649 or placebo in a ratio of 7:2 (7 active, 2 placebo). Safety, PK and PD data from the initial cohorts will be assessed, to determine whether to initiate a fifth dosing cohort at a dose not to exceed 20 mg/kg. Eligible subjects will report to the Clinical Pharmacology Unit (CPU) at study check-in (Day -1) and will be required to stay in the CPU until Day 2 (24 hours post infusion). On Day 1, a single dose of VIS649 or placebo will be administered IV in the morning after a light meal (as per the clinical unit standard). Pharmacokinetics sampling will occur on Day 1 starting with a collection 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. Pharmacokinetics samples will also be drawn

	on Days 3, 7, 14, 28, 42, 56, 70, and 112. Pharmacodynamics sampling (serum immunoglobulin levels) will occur at Baseline, Day 3 and weekly thereafter through the Week 8 visit, then once every two weeks through Week 16 (i.e., Weeks 10, 12, 14, and 16). Sentinel subjects will be utilized; 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. The safety profile of these subjects over the 24 hour post-administration period will be reviewed to determine whether it is appropriate to proceed with enrollment of the remaining subjects in the cohort as planned. This will occur for each dose escalation. The remaining 7 subjects in each cohort will be randomized to receive VIS649 (n=6) or matched placebo (n=1). The maximum duration of participation (Screening through End-of-study) for individual subjects will be approximately 20 weeks (5 months) with the possibility to extend up to 28 weeks (7 months). Each subject will participate in screening period lasting 1 to 28 days (0 to 4 weeks), an in-house stay for 2 to 3 days, and a post-administration period of 16 weeks. The scheduled final visit will occur 16 weeks post-dosing (112 days); however, two additional follow-up visits may be performed, at Weeks 20 and 24 post-dosing, if serum immunoglobulins have not returned to>lower limits of normal by the Week 16 visit or if emerging trial data suggest a value of later follow-up (i.e., for detection of anti-drug antibody responses).
Investigational Medicinal Product	A single dose of VIS649 administered IV over approximately one hour, at four different dose levels: 0.5, 2.0, 6.0 and 12 mg/kg, with an optional fifth cohort, to receive up to but not exceeding 20 mg/kg.
Number of Subjects	Up to 45 subjects may be enrolled. A total of 20 Japanese subjects (4 subjects per cohort) and 25 non-Japanese subjects (5 subjects per cohort) may be enrolled and randomized to receive a single dose of VIS649 or placebo. No more than one Japanese subject per cohort, may be randomized to receive placebo. Safety, PK and PD data from the initial four dosing cohorts will be assessed, to determine whether to initiate a fifth dosing cohort at a dose not to exceed 20 mg/kg.
Study Population	Healthy, non-smoking male and female subjects, 18 to 55 years of age with a body mass index between 18 and 32 kg/m^2, are planned for enrollment.
Criteria for Evaluation	*Safety Endpoints* 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 assessed from the time of study drug administration to the end-of-study participation: • Adverse event assessments • Clinical laboratory tests (hematology, clinical chemistry and urinalysis) • Vital signs (sitting blood pressure, pulse, body temperature and respiratory rate), • Twelve-lead electrocardiogram (ECG) • Adjunctive procedures • Physical examination *Secondary Endpoints* • Characterization of anti-drug antibodies (ADA) levels *Pharmacokinetics Endpoints*

	The following pharmacokinetics 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-inf}: Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinite time [redacted] • $t_{1/2}$: Apparent terminal elimination half life • Vd: Apparent volume of distribution [redacted] • CL: Apparent clearance [redacted] *Pharmacodynamics Endpoints* • Changes in total serum IgG, IgA and IgM concentrations and time to recovery • Changes in whole blood circulating lymphocyte populations [redacted]
Statistical Methods	*Sample Size Considerations* As this is a first-in-human study and no clinical data are available, no formal sample size calculations have been performed. A total of up to 45 evaluable subjects is considered suitable to achieve the study objectives. *Data Presentation/Descriptive Statistics* In general, descriptive statistics for continuous variables will be summarized by treatment group using number of subjects, arithmetic mean, standard deviation, median, minimum and maximum; descriptive statistics for categorical data will be summarized by treatment group using frequency counts and percentages. Summary of demographics and safety data will be analyzed using descriptive statistics as appropriate. The VIS649 serum concentrations will be listed and summarized by dose and time-point. Individual and mean VIS649 concentration-time profiles will be plotted in linear and semi-log scales. Non-compartmental PK data analysis will be performed for VIS649 treated subjects to estimate the AUC_{0-inf}, C_{max}, T_{max}, t½, CL and Vd. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, standard deviation, arithmetic coefficient of variation (%CV), and geometric mean, median, geometric %CV, minimum and maximum. [redacted] The number and percentage of subjects that are ADA positive will be summarized by dose. The impact of ADA on PK and the association with treatment-emergent adverse events and treatment-emergent serious adverse events will be assessed. PD data will be assessed using change from baseline data and % change from baseline, as appropriate. The PK/PD relationship between investigational

	medicinal product exposure and exploratory endpoints may also be analyzed by graphical displays if Sponsor requests. All demographic, safety, PK, and PD data will be listed. Full details of the data analysis will be provided in a separate statistical analysis plan.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
a-g IgA	Aberrantly glycosylated IgA (synonymous with GD IgA)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APRIL	A Proliferation Inducing Ligand
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinite time ($AUC_{last} + C_{last}/\lambda_z$)
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CL	Apparent clearance
C_{max}	Maximum serum concentration
CPU	Clinical Pharmacology Unit
CRO	Clinical Research Organization
CSR	Clinical Study Report
CV	Coefficient of variation
CVID	Common variable immunodeficiency
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FDA	Food and Drug Administration
Fe	Percentage of drug excreted unchanged in the urine
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GD IgA	Galactose deficient IgA (synonymous with a-g IgA)
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act

HIV	Human Immunodeficiency Virus
HBsAg	Hepatitis B surface antigen
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgAN	IgA nephropathy
IgG_2	Immunoglobulin G
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
KLH	Keyhole limpet hemocyanin
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimum Intolerable Dose
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
OTC	Over-the-counter
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure
SID	Subject identification
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard operating procedure
TACI	Transmembrane activator and CAML interactor
$t_{½}$	Terminal elimination half-life

T_{max}	Time of maximum serum concentration
US	United States
ULN	Upper level of normal
Vd	Apparent volume of distribution
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

VIS649 is a humanized immunoglobulin G (IgG_2) monoclonal antibody that binds to and blocks the biological actions of the B-cell growth factor, APRIL (A Proliferation Inducing Ligand), preventing binding to its receptors, transmembrane activator and CAML interactor (TACI) and B-cell maturation antigen (BCMA). Through these receptor interactions, APRIL regulates B-cell-mediated immune responses through several mechanisms, including the induction of class switch recombination as well as promotion of plasma cell survival. [redacted]

[redacted]

VIS649 binds human APRIL with picomolar affinity/avidity as measured by antigen-binding enzyme-linked immunosorbent assay using recombinant trimeric APRIL. VIS649 blocks recombinant APRIL-APRIL receptor interactions, thereby inhibiting APRIL-mediated signaling and B cell proliferation. VIS649 also binds cynomolgus monkey APRIL, with similar affinity and inhibition of APRIL mediated signaling in both species. The physiological and toxicological effects of VIS649 were therefore evaluated in cynomolgus monkeys, in three pre-clinical studies.

In an initial non- Good Laboratory Practice (non-GLP) *in-vivo* toxicology study, weekly administration of IV VIS649 at a dose of 25 mg/kg for 8 weeks resulted in an approximately 70% reduction in serum IgA levels (in comparison with control animals) with minimal effect on serum IgM, and an approximately 40% reduction in serum IgG levels. Hematology assessment did not reveal significant perturbation in white blood cell (WBC), lymphocyte, or leukocyte counts and there were no significant differences between treatment groups noted in the peripheral blood and tissue immune profiling, which included markers for total T cells, helper T cells, cytotoxic T cells, natural killer cells, and B cells. In a subsequent, non-GLP dose range-finding study, VIS649 was

administered weekly over 4 weeks to groups of cynomolgus monkeys at doses of 0 (control), 0.5, 2.5, and 10 mg/kg, with an 8-week recovery observation period. Following treatment with 0.5 and 2.5 mg/kg doses, there was a [redacted] reduction from baseline in serum IgA levels. Monkeys treated with 10 mg/kg doses had a [redacted] reduction in serum IgA levels, similar to the effect observed in the prior study with 25 mg/kg dosing for 8 weeks, and thus providing evidence that APRIL inhibition does not completely suppress IgA production. Serum IgA level suppression was reversible, with a dose response in time-to-recovery during the 8-week follow-up period. The observation of a maximal suppressive effect of VIS649 on serum IgA levels [redacted] in monkeys was further supported in the third toxicology study, described below. There was a lesser effect of VIS649 on serum IgG levels [redacted] and IgM levels were not altered notably, in comparison with control animals. Peripheral blood lymphocyte counts were not significantly affected, including the following cell populations: T-lymphocytes (including T-helper and cytotoxic T-cell subsets), natural-killer cells, monocytes, and B-lymphocytes (including naïve, resting memory and activated memory B-lymphocyte subsets).

These studies led to the conduct of a United States Food and Drug Administration (US FDA) GLP-compliant 4-week repeat-dose IV toxicology study of VIS649 in cynomolgus monkeys, with a 20-week recovery period. Monkeys received weekly VIS649 injections for 4 weeks, at doses of 0 mg/kg (control), 25 mg/kg, 50 mg/kg, or 100 mg/kg.

VIS649-related reductions in total serum IgA levels were observed in all VIS649-treated animals [redacted] and the reductions were reversible as trends towards return to baseline were observed at all doses. All 3 dose levels demonstrated maximal pharmacologic effect that were consistent with previous studies in reduction in serum IgA and IgG levels with a minimal effect on IgM levels in VIS649 treated animals in comparison to the controls.

Serum IgG levels were moderately reduced, [redacted] for a majority of animals at all timepoints. Serum IgM concentrations did not differ significantly between groups, including control animals.

There was no effect of VIS649 on measured plasma cytokine concentrations in the monkey toxicology studies (nor did VIS649 stimulate significant cytokine release in an *in vitro* human peripheral blood lymphocyte cytokine release assay).

To test the effect of VIS649 on de-novo humoral immune responses to a novel (T-cell dependent) antigen challenge, monkeys were vaccinated with keyhole limpet hemocyanin (KLH) at Day 7 during dosing, with measurement of KLH-specific IgG and IgM levels through 21 days post

immunization. The kinetics of IgM and IgG responses were similar between VIS649 treated and control animals, with moderate suppression of KLH-specific IgG levels which was consistent with the non-specific suppression seen in total IgG levels.

Based on results from this pivotal toxicology study, the no-observed-adverse-effect level (NOAEL) was considered to be 100 mg/kg/dose [redacted]. The 100 mg/kg dose is 5-fold greater than the highest dose (20 mg/kg) permitted in this first-in-human study and 200-fold greater than the lowest dose (0.5 mg/kg) to be administered in this FIH study.

[redacted]

The relatively selective and reversible effect of VIS649 on serum immunoglobulin levels [redacted] with maximal (but not completely suppressive) effect on IgA suggests that APRIL inhibition may be uniquely suited as a therapeutic strategy for IgA nephropathy.

Further details can be found in the IB [2].

1.2. Rationale for the Clinical Study

This first-in-human (FIH) study will assess the safety and tolerability, pharmacokinetics (PK)/pharmacodynamics (PD) of VIS649, a humanized IgG_2 mAb that binds to and blocks the biological actions of the B-cell growth factor, APRIL.

The study is being conducted to establish a dose range that is well tolerated by the majority of study subjects and to provide exploratory data on the potential for the treatment of IgAN, an autoimmune glomerulonephritis characterized by the deposition of IgA-containing immune complexes in the kidney. The results of the clinical study will inform the design and dose selection of subsequent studies.

1.3. Risk-benefit Assessment

While VIS649 has not been evaluated in humans, the known effects of mAbs in humans suggest the following potential toxicities for single dose administration:

1. Infusion reactions: Anaphylaxis, fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, and chest pain
2. Delayed allergic reactions: Serum sickness (i.e., urticaria, fever, general glandular enlargement, joint pains)
3. General: Injection site reaction

Mechanism based potential toxicities that might be anticipated based on VIS649 mechanism of action and preclinical studies include:

IgA suppression risks: VIS649 treatment is expected to reduce human IgA levels, with a predicted maximal reduction (with repeated dosing) to approximately 75% below baseline. In this single-ascending dose study, this degree of suppression is unlikely to be achieved, but it is anticipated that at least in the higher dose cohorts, IgA levels will be reduced below baseline, with effect persisting over weeks.

The normal range for serum IgA is approximately 70 to 400 mg/dL in adults [redacted]

Selective IgA deficiency (defined as persistently undetectable IgA, [redacted]) is the most common inherited immunodeficiency syndrome (occurring in about 1 in 500 Caucasian individuals). [3]. While this condition has heretofore been considered generally benign and is asymptomatic in the majority of patients, there is increasing recognition that selective IgA deficiency may be associated with recurrent sinopulmonary infection, allergy, autoimmunity and gastrointestinal microbiome perturbation [4, 5]. The risk for occurrence of these complications in the current study is low for multiple reasons: 1) IgA is expected to be suppressed, but not reduced to undetectable levels, 2) in this single dose-study, the effects on IgA levels are expected to be transient, and 3) the syndrome of selective IgA deficiency is often associated with additional immunologic impairments including T-cell disorders and common variable immunodeficiency syndrome.

IgG suppression risks: VIS649 is expected to have a moderate effect on serum IgG levels (with approximately 40% suppression-below-baseline nadir values predicted).

The normal range for serum IgG is approximately 600 to 1600 mg/dL in adults, [redacted]

In common variable immunodeficiency (CVID), also known as acquired hypogammaglobulinemia, total IgG levels are typically below 250 mg/dL with median values at diagnosis in two recent U.S. cohort studies of 210 mg/dL and 120 mg/dL, respectively [6]. The condition is of heterogenous origin, with loss of function mutations in an APRIL receptor, TACI, identified as one causal association [7]. Proposed diagnostic criteria for CVID include: presence of hypogammaglobulinemia [redacted] plus a history of recurrent or chronic infection or autoimmunity and with associated IgA deficiency [redacted] or IgM deficiency [redacted] [8]. Common variable immunodeficiency is associated with recurrent otitis media, chronic sinusitis, and recurrent pneumonia often resulting in bronchiectasis [9]. Longitudinal studies have demonstrated high rates of lymphoma and diseases of autoimmunity [10]. The risk of these complications in the current study is considered quite low, given the moderate and transient reductions in IgG levels that are anticipated.

Non-specific immunosuppression risks: In preclinical toxicology studies, de-novo humoral immune responses to a novel antigen were not suppressed, and peripheral blood myeloid cell line populations were unaffected. However, there is the possibility of non-specific immunodeficiency with potential risk of exacerbation of pre-existing latent infection or poor response to new infection. These risks are considered minimal due to the single-dose design of this trial, and the expected transient nature of effects.

Pharmacodynamic data including measurement of changes in serum IgG, IgA, and IgM levels in relation to VIS649 exposure will provide valuable information for refinement of the human PK/PD model and selection of appropriate doses for a repeat-dose study. Predicted maximal effects on serum IgG, IgA and IgM levels versus normal range, inclusion criteria thresholds, and stopping rule IG thresholds are summarized in Table 1.

Table 1 Serum Immunoglobulin Normal Ranges, Inclusion Criteria, Predicted Maximal Nadirs, and Stopping Rule Thresholds

Immunoglobulin Class	Serum Concentration Normal Range in Adults [1]	[redacted]	[redacted]	[redacted]
IgA	66-433 mg/dL [0.66-4.33 g/L]	[redacted]	[redacted]	[redacted]
IgG	635-1741 mg/dL [6.35-1.74 g/L]	[redacted]	[redacted]	[redacted]
IgM	45-281 mg/dL [0.45-2.81 g/L]	[redacted]	[redacted]	[redacted] or more patients

[1] Immunoglobulin reference ranges for healthy adult volunteers from the laboratory performing these tests for the study (GenX Lab), as measured with a Beckman Coulter Analyzer, instrument AU480.

[redacted]

There will be no direct health benefit for healthy subjects from receipt of the study drug. The protocol has been designed to minimize the risk to research participants. Subjects will be monitored to detect adverse events (AE)s during the study and followed appropriately to ensure resolution of AEs. Sentinel dosing will be employed within each cohort, and available blinded safety data will be assessed after each dose level to determine if it is safe to escalate to the next planned dose.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the safety and tolerability of VIS649 in healthy subjects.

2.2. Secondary Objectives

- To characterize the PK profile of VIS649
- To evaluate the effect of race on the pharmacokinetic profile of a single intravenously (IV) 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 PD parameters including:
    - changes in serum total IgA, IgG and IgM concentrations and time to recovery
    - changes in whole blood circulating lymphocyte populations

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1. Overview

This is a phase 1, randomized, placebo-controlled, double-blind, 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 four sequential dosing cohorts enrolling nine subjects per cohort, with an optional fifth cohort. Each cohort will have 4 Japanese subjects. Subjects will be randomized to VIS649 or placebo in a ratio of 7:2 (7 active, 2 placebo). No more than one Japanese subject per cohort may be randomized to receive placebo. Safety, PK and PD data from the initial cohorts will be assessed, to determine whether to initiate a fifth dosing cohort at a dose not to exceed 20 mg/kg.

The study comprises of:

- A Screening Visit up to 28 days before dosing
- An in-house stay for approximately 2-3 days, with admission to the study center on Day -1, dosing on Day 1, and discharge in the morning of Day 2
- A post-administration period of 16 weeks
- Outpatient visits, on Day 3 (+1 day), 7 (± 1 day), 14, 21, 28, 35, 42, 49, 56, 70, 84 and 98 (all visits± 3 days)
- A final Follow-up visit on Day 112 (± 3 days); Two additional follow-up visits may occur, at Weeks 20 and 24 post-dosing, if serum immunoglobulins have not returned to >lower limits of normal by the Week 16 (Day 112) visit, or if emerging trial data suggest a value of later follow-up (i.e., for detection of ADA responses).

The total duration of the clinical study per subject will be up to approximately 20 weeks (5 months), including the Screening period with the possibility of duration extending to 28 weeks (7 months) if follow-ups visits are required.

Potential subjects will be carefully screened for eligibility prior to study enrollment. Randomization and blinding will occur according to a core randomization list administered by the site's unblinded pharmacist.

Eligible subjects will report to the Clinical Pharmacology Unit (CPU) at study check-in (Day -1) and will be required to stay in the CPU until Day 2 (24 hours post infusion). On Day 1, a single

dose of VIS649 or placebo will be administered intravenously in the morning after a light meal (as per the clinical unit standard). Pharmacokinetics sampling will occur on Day 1 starting with a collection prior to the start of infusion, end of infusion, and at 2 hours, 8 hours and 24 hours post end of infusion. Pharmacokinetics samples will also be drawn on Days 3, 7, 14, 28, 42, 56, 70, and 112. Pharmacodynamics sampling (serum immunoglobulin levels, lymphocytes and sub Ig types) will occur as outlined in the Schedule of Assessments (Table 9).

The initial cohort will be dosed with 0.5 mg/kg of VIS649. Escalation to next dosing level (2.0 mg/kg) will occur after review of blinded safety data through Day 14 by the Safety Monitoring Committee (SMC) comprised of the Investigator, an independent Medical Monitor, and the Sponsor. For subsequent cohorts (6.0 mg/kg and 12 mg/kg, and the optional fifth dosing cohort), escalation will occur after review of safety data through Day 28 by the SMC. Assessment of safety will be determined by evaluation of:

- Vital sign measurements
- Physical examinations
- Hematology, chemistry, and urinalysis laboratory testing
- 12-lead electrocardiograms (ECG)
- Adverse events, and
- Serum immunoglobulin levels

Pharmacokinetic data will not be available for dose escalation decision making. Pharmacokinetic data will be reviewed in a blinded fashion after each cohort is available, and may result in a dose adjustment for subsequent cohorts (including optional cohort 5, and none to exceed 20 mg/kg). Any adjustments will be reviewed and approved by the Investigator, Medical Monitor, and the Sponsor.

If dose escalation is stopped based on available blinded safety data, the current dose level will be considered as the minimum intolerable dose (MID). The dose just below the MID will be regarded as the maximum tolerated dose (MTD). If the dose escalation is stopped due to reaching exposure limit without dose limiting safety findings, the MTD will not be determined. Dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels.

Stopping rules are described in Section 3.4.

Procedures related to the clinical study are detailed in the Schedule of Assessments (Table 9).

Doses will be administered intravenously to subjects in approximately 4 dose cohorts (see Table 2). An additional cohort may be enrolled and proceed at a dose not to exceed 20 mg/kg (given the safety coverage described in Section 5.2), if deemed appropriate by the SMC. 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[1]
	N=2	Placebo
Cohort 2	N=7	VIS649 2.0 mg/kg[2]
	N=2	Placebo
Cohort 3	N=7	VIS649 6.0 mg/kg[2]
	N=2	Placebo
Cohort 4	N=7	VIS649 12 mg/kg[2]
	N=2	Placebo
Optional Cohort 5	N=7	VIS649 TBD, not >20 mg/kg
	N=2	Placebo

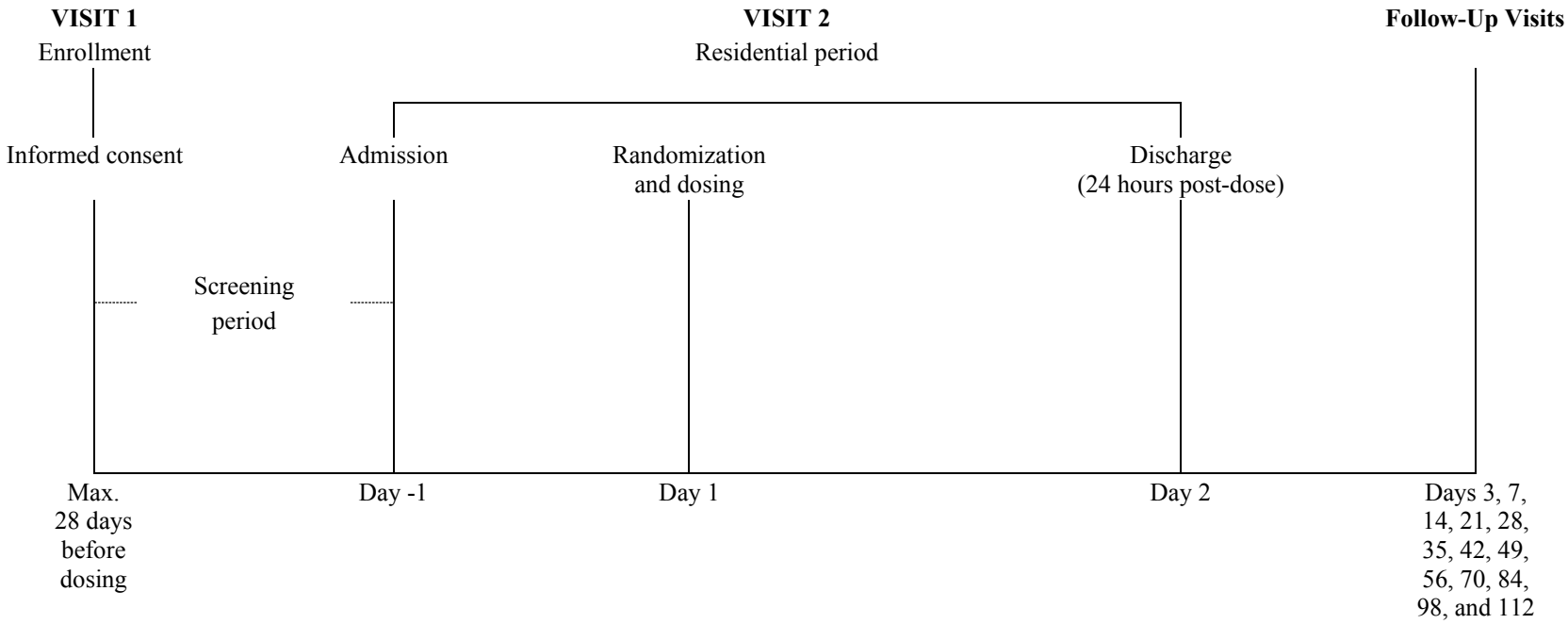
TBD: To be decided

[1]After all subjects have completed assessments through Day 14, blinded safety data will be reviewed and a dose escalation decision for the subsequent cohort will be made by the SMC. If dose escalation is stopped, dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels.

[2] After all subjects have completed assessments through Day 28, blinded safety data will be reviewed and a dose escalation decision for the subsequent cohort will be made by the SMC. If dose escalation is stopped, dose de-escalation may occur in additional cohorts, to further refine clinically relevant dose levels.

Please refer to Table 9 for a detailed list of procedures performed on each study day and visit.

Figure 1 Study Flow Chart – Single Ascending Dose Design



3.2. Endpoints

3.2.1. 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, pulse, body temperature and respiratory rate [RR])
  - Twelve-lead ECG
  - Adjunctive procedures
  - Physical examination

3.2.2. Secondary Endpoints

- Characterization of anti-drug antibodies (ADA) levels

3.2.2.1. 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
- $AUC_{0\text{-}inf}$: Area under the concentration-time curve from pre-dose (time 0) extrapolated to infinite time [redacted]
- $t_{1/2}$: Apparent terminal elimination half life
- Vd: Apparent volume of distribution [redacted]
- CL: Apparent clearance [redacted]

3.2.2.2. Pharmacodynamics Endpoints

- Changes in total serum IgG, IgA and IgM concentrations and time to recovery
- Changes in whole blood circulating lymphocyte populations

[redacted]

3.3. Justification of the Study Design

This study evaluates the safety, tolerability, and PK/PD of ascending single doses of VIS649 administered as an IV infusion. The design is standard and is considered appropriate to meet the objectives of the study.

A double-blind, placebo-controlled study is appropriate and standard for a single ascending dose study. This design will minimize bias and provide reference data (i.e., data from placebo-treated subjects) which will aid in the interpretation of results. The SMC will review available blinded safety, tolerability, and Ig level data after each cohort to confirm whether it is safe to proceed with the next planned dose, whether the dose escalation should be stopped or if the dose should be lowered, repeated, or titrated in the subsequent cohort.

The safety assessments for the study are accepted measures for ensuring safety of subjects during a clinical trial. The PK sampling schedule is considered appropriate given the information available. The rationale for dose selection is discussed in Section 5.2.

3.4. Stopping Criteria for the Clinical Study and Dose Escalation Criteria

If any of the dose limiting toxicities listed below are met, the relevant subject(s) data may be unblinded. If the toxicity is present in ≥ 1 subject randomized to active drug, then dose escalation will pause. Depending upon the nature of the event, a decision may be made to resume dosing, to proceed into the next cohort at a lower dose level, or to stop the study.

Based on safety criteria, the dose adjustment/stopping criteria are as follows:

- Adverse event stopping criteria:

  - Any AE of severe intensity and related causality
  - Any SAE of related causality

- Vital sign stopping criteria:
  - Symptomatic hypotension (systolic blood pressure [SBP] <85 mmHg). If symptomatic hypotension that is related to the study drug is observed during the study, then a minimum of two repeat BP measurements should be obtained over a brief period. The mean of the three SBP measurements will be used to determine stopping criteria.
  - Tachycardia defined as heart rate >120 beats per minute (bpm) lasting longer than 30 minutes or with impaired consciousness
- Electrocardiogram stopping criteria:
  - QT interval [redacted] >500 msec (If a prolonged QTc interval is observed during the study, then a minimum of two repeat ECGs should be obtained over a brief period. The mean of the three ECGs will be used to determine stopping criteria.)
- Clinical laboratory stopping criteria:
  - Alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN)
  - Aspartate aminotransferase (AST) ≥3 times the ULN
  - Serum creatinine >1.5 times the ULN
  - A decrease from Baseline in hemoglobin concentration >3 g/dL
  - White blood cell count <1,500/mm^3
  - Platelets <50,000/mm^3
  - Persistent serum IgA reduction to <15 mg/dL (with at least two measurements over at least one week apart) in ≥2 patients
  - Persistent serum IgA reduction to <7 mg/dL (or below local laboratory limit of detection) (with at least two measurements, at least one week apart) in any single patient
  - Persistent serum IgG reduction to <300 mg/dL (with at least two measurements, at least one week apart) in ≥2 patients
  - Persistent serum IgM reduction to <25 mg/dL (with at least two measurements, at least one week apart) in ≥2 patients.

4. STUDY POPULATION

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

4.1. Number of Subjects

Up to 45 subjects may be enrolled in this clinical study. Up to 20 Japanese subjects (4 subjects per cohort) and up to 25 non-Japanese subjects (5 subjects per cohort) will be enrolled (N=9 per dose cohort) and randomized to receive a single dose of VIS649 (N=7) or placebo (N=2) across up to five cohorts. No more than one Japanese subject per cohort may be randomized to receive placebo. The fifth dosing cohort is considered optional: safety, PK and PD data from the initial cohorts will be assessed, to determine whether to initiate dosing in this cohort at a dose not to exceed 20 mg/kg.

4.2. Inclusion Criteria

Subjects who meet the following criteria will be considered eligible to participate in the clinical study:

1. Subject voluntarily agrees to participate in this study and signs an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent form prior to performing any of the Screening Visit procedures and be able to sign and date an appropriate Health Insurance Portability and Accountability Act (HIPAA) authorization form or subject privacy form, if appropriate.
2. Male and female subjects between 18 to 55 years of age, inclusive, at the Screening Visit.
3. For Japanese subjects: Subject is of Japanese descent as evidenced by verbal confirmation of familial heritage (a subject has all four Japanese grandparents born in Japan).
4. For non-Japanese subjects: Subjects must be of non-Asian descent, as evidenced by verbal confirmation that all four grandparents are non-Asian.
5. The following applies to female subjects:
    - Non-childbearing potential (surgically sterile [hysterectomy or bilateral tubal ligation]) for at least 6 months, or postmenopausal ≥ 1 year, or
    - Non-pregnant, non-lactating females of childbearing potential must report prior use (over the 28 days prior to dosing of study drug) of medically acceptable forms of birth control (hormonal contraception, abstinence, diaphragm with spermicide, condom with spermicide

or intrauterine device, or partner with vasectomy), with agreement to continue to use a medically acceptable form of birth control (as described) through the end of their participation in the study. Alternatively, a reported history of abstinence beginning at least 28 days prior to study drug dosing, with agreement to continue abstinence through the end of their participation in the study are required. Females of childbearing potential must also have a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at Baseline (Day -1). Female subjects must also agree not to donate eggs/bank eggs for the duration of their participation in the study.

6. For male, subject and/or his partner must use a highly effective form of contraception (i.e., double-barrier as described above, have had a vasectomy, or have a female partner of non-childbearing potential) or agree to abstinence following study drug dosing, through the end of the subject's participation in the study. Male subjects must also agree to not donate sperm for the duration of their participation in the study, following study drug dosing.
7. Screening laboratory values must meet the following criteria:
   - White blood cells 3,000-12,000/mm^3
   - Platelets >150,000/mm^3
   - Hemoglobin >13 gm/dL for male and>11 gm/dL for female
   - Estimated glomerular filtration rate >80 mL/min/1.73 m^2
   - Serum creatinine <1.25x ULN
   - Blood Urea Nitrogen (BUN) ≤25mg/dL
   - Aspartate aminotransferase (AST) ≤50 U/L
   - Alanine aminotransferase (ALT) ≤67 U/L
   - Alkaline phosphatase ≤150 U/L
   - Total Bilirubin ≤1.4 mg/dL

     unless patient has Gilbert Syndrome, in which case direct bilirubin must be within normal range
   - Glucose (fasting) <115 mg/dL
   - Drug and alcohol screen Negative

[redacted]

[redacted]

8. Body mass index (BMI) between 18 and 32 kg/m^2, inclusive, at the Screening Visit.
9. Healthy, determined by pre-study medical evaluation (medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluations), as judged by the Investigator.
10. Is willing and able to comply with study restrictions and to remain at the CPU for the in-patient duration of the study and return for all follow-up outpatient visits.
11. QTcF or QTcB < 450 msec at Screening (may be repeated once).

4.3. Exclusion Criteria

Subjects who meet one or more of the following criteria will not be considered eligible to participate in the clinical study:

1. Is participating in another clinical study of any investigational drug, device, or intervention or has received any investigational medication during the last 30 days or five half-lives, whichever is longer, before Baseline (Day -1).
2. Subject is judged by the Investigator or the Medical Monitor to be inappropriate for the study.
3. Subject has a history or current evidence of a serious and/or unstable cardiovascular, respiratory, gastrointestinal, hematologic, autoimmune, blood dyscrasias or other medical disorder, including psychiatric disorders, cirrhosis or malignancy. History of minor skin cancers (not including melanoma) or surgically treated, limited cervical carcinomas (i.e., carcinoma in situ) are not exclusionary.
4. Subject has a history or presence of proteinuria, chronic kidney disease, disease requiring immunosuppressive therapy (including systemic steroids), or is considered to be immunosuppressed for any other reason.
5. Previous receipt of antibody or biologic therapy whether licensed or investigational (immunoglobulin products, monoclonal antibodies or antibody fragments) within 30 days prior to dosing or 5 half-lives within the dose of Investigational medicinal products (IMP), whichever is longer.
6. History of a previous severe allergic reaction with generalized urticaria; angioedema or anaphylaxis.
7. Blood pressure >160/100 mmHg or <90/50 mmHg (may be repeated once if abnormal), at the Screening visit and Day -1.

8. Known hypoglobulinemia disorder (i.e., common variable immunodeficiency), X-linked agammaglobulinemia, selective IgA deficiency, selective IgM deficiency).
9. History of pre-existing latent infections (e.g., tuberculosis) or any infection requiring hospitalization or treatment with antivirals or antibiotics, or vaccination within 30 days prior to administration of study medication.
10. Concomitant use of marketed or investigational systemic immunosuppressive or immunomodulatory medications (e.g., corticosteroids, methotrexate, azathioprine, etc. and/or biologics) is prohibited and require a washout period prior to Screening (30 days or 5 half-lives, whichever is longer).
11. Has received any prescription or non-prescription (over-the-counter [OTC]) except acetaminophen or ibuprofen, including hormonal contraceptives, topical medications, vitamins, dietary or herbal during the last 30 days or 5 half-lives, whichever is longer, preceding Baseline (Day -1).
12. Subjects who consume more than 21 units of alcohol per week (7 days) or those who have a history of alcohol or drug/chemical abuse; one unit of alcohol is equivalent to eight ounces of beer, 4 ounces of wine, or one ounce of spirits.
13. Subject is a user or former user of nicotine-containing products (including but not limited to cigarettes, cigars, and chewing or dipping tobacco) who stopped use or consumption (i.e., smoking, chewing, or pinching) of these nicotine-containing products less than 3 months before study drug administration or is using or has used topical or oral nicotine preparations for smoking cessation within the past 90 days before study drug administration.
14. Subjects who consume greater than 500 mg of caffeine or xanthine-containing products per day (e.g., coffee, tea, soft drinks, energy drinks, or chocolate).
15. Subjects who refuse to abstain from alcohol, xanthine-containing or caffeine-containing foods or beverages, or grapefruit foods or beverages, or Seville-orange containing foods (e.g., orange marmalade) or beverages, from 48 hours prior to check-in on Day-1 through the end of the study.
16. Subjects with a positive urine drug (inclusive of marijuana) or alcohol Screening test result at Screening and Day -1.
17. Subjects with a positive hepatitis B surface antigen test or evidence of chronic hepatitis C virus infection at Screening (a negative HCV antibody assay at screening is sufficient to rule-out chronic HCV infection for this study).

18. Subjects with a known history of a positive Human Immunodeficiency Virus (HIV) or a positive test result at Screening.
19. Subjects who have donated >500 mL or blood within 60 days prior to start of Screening.
20. The subject has donated any plasma within 7 days prior to Baseline (Day -1).
21. Is an employee of the clinical research team (any Visterra or research site employee), or has a family member who is an employee of these organizations.

4.4. Subject Withdrawal and Replacement

While subjects are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any subject withdraws from the study prematurely. 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:

1. Adverse event
2. Protocol violation
3. Loss to follow-up
4. Subject withdrew consent at own request
5. Other

A genuine effort must be made to determine the reason(s) why a subject fails to return for the necessary visits or is discontinued from the study. If the subject is unreachable by telephone, a registered letter, at the minimum, should be sent to the subject requesting him/her to contact the clinic.

Subjects can be replaced, and a replacement randomization number will be generated. The same treatment will be allocated to the replacement subject.

4.5. Termination of the Clinical Study

If the Principal Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. 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.

Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and VIS649 must be returned to the Sponsor. Any actions of PAREXEL required for assessing or maintaining subject safety will continue as required, despite termination of the study by the Sponsor.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. Identity of the Investigational Medicinal Products

The investigational products that will be used in this study are outlined in Table 3.

Table 3 Identity of Investigational Products

Drug Name	Formulation	Strength	Route	Manufacturer
VIS649	Solution (to be diluted into a final volume of 100 mL 0.9% NaCl)	25 mg/mL [redacted]	IV	Sponsor
Placebo	Solution	0.9% NaCl	IV	To be sourced by PAREXEL

IV: intravenous; NA: not applicable; NaCl: Sodium Chloride
Data source: Investigator Brochure

5.2. Rationale for Starting Dose and Dose Escalation

VIS649 will be administered at a first-in-human starting dose of 0.5 mg/kg IV to healthy volunteers. The starting dose was selected upon consideration of the VIS649 target and mechanism of action, *in vitro*/*in viv*o toxicology data, the NOAEL observed in the pivotal toxicology study in cynomolgus monkeys, and estimations derived from a PK/PD model of the pharmacologically active dose in humans. In each dosing cohort, two subjects (one receiving placebo, the other receiving VIS649) will be dosed 24 hours before others in the respective cohort, to provide a sentinel function should unanticipated adverse reactions occur at any dose level.

The cynomolgus monkey is considered a relevant species for evaluation of VIS649 toxicity due to similarity in B cell biology, 99% sequence homology between cynomolgus and human APRIL, and similar binding affinity of VIS649 to cynomolgus and human APRIL (within ~2-fold). The effects of multiple doses of VIS649 were evaluated in a GLP toxicology study in healthy cynomolgus monkeys at 25, 50, and 100 mg/kg IV once weekly over 28 days. VIS649 was well tolerated in cynomolgus monkeys with no VIS649-related clinical findings up to 100 mg/kg; the NOAEL from this study was 100 mg/kg.

A maximum recommended starting dose of 5 mg/kg was identified by considering the NOAEL of 100 mg/kg in cynomolgus monkeys, which translates to a human equivalent dose of 100 mg/kg for monoclonal antibody therapeutics. Applying a safety factor of 2X that accounts for the measured affinity difference of VIS649 for monkey and human APRIL, and an additional 10X

safety factor to account for potential interspecies differences and other unknowns arrives at a NOAEL justified starting dose of 5 mg/kg, which is expected to be well tolerated in humans based on cynomolgus monkey studies.

[redacted]

[redacted]

The minimum pharmacologically active dose of 0.5 mg/kg was selected as the starting dose for evaluation in healthy volunteers; this is 10-fold lower than the maximum recommended starting dose based on the NOAEL. Doses from 0.5 to 12 mg/kg will be evaluated in single dose escalation in four cohorts, while a final cohort to receive a dose greater than 12 mg/kg but no greater than 20 mg/kg may be enrolled, based on emerging clinical, PK and/or PD data. Dose escalations will not exceed a 4-fold increase. The safety margins for targeted clinical doses are provided in Table 4.

[redacted]

Simulations using the previously described PK model [2] were performed under the conservative assumption of zero nonlinearity for the purpose of the safety margin calculation. [redacted]

5.3. Supply, Packaging, Labeling and Storage

Investigational medicinal products will be packaged and labeled according to applicable local and regulatory requirements.

VIS649 is formulated at a concentration of 25 mg/mL [redacted] will be supplied in vials containing a nominal 10 mL.

All supplies of study drug VIS649 must be stored between≥2°C and ≤8°C and protected from light. The study drug VIS649 will be stored in a securely locked area, accessible to authorized persons only.

5.4. Drug Accountability, Dispensing and Destruction

The Principal Investigator or designee is responsible for maintaining accurate accountability records of the study drug throughout the clinical study. The drug accountability log includes

information such as, randomization number, amount dispensed and amount returned to the pharmacy (if any). Products returned to the pharmacy will be stored under the same conditions as products not yet dispensed. The returned products should be marked as 'returned' and kept separate from the products not yet dispensed.

All dispensing and accountability records will be available for Sponsor review. When the Study Monitor visits PAREXEL, he/she will reconcile the drug accountability log with the products stored in the PAREXEL pharmacy.

The PAREXEL pharmacist (or designee under the direction of the pharmacist) will dispense study drug in a blinded manner for each subject according to the protocol, randomization list and pharmacy manual, if applicable.

After receiving Sponsor approval in writing, PAREXEL is responsible for returning all unused or partially used study drug to the Sponsor or designated third party or for preparing the study drug for destruction via incineration.

5.5. Subject Identification and Randomization

5.5.1. Screening Numbers

All screened subjects are assigned a unique 3-digit subject identification (SID) number (001 - 999). The SID numbers identify subjects from time of Screening until time of randomization. Enrolled subjects who drop out of the clinical study before randomization will retain their SID numbers.

5.5.2. Randomization numbers

Prior to dosing on Day 1, eligible subjects will be assigned a randomization number in accordance with the randomization code generated by PAREXEL International. The randomization code will be maintained in a room with restricted access to pharmacy personnel only. The randomization code will include 4-digit subject numbers [redacted] Cohort and randomization numbers list in Table 5.

Table 5 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			2.0 mg/kg VIS649 (N=7)	Placebo (N=2)
Cohort 3			6.0 mg/kg VIS649 (N=7)	Placebo (N=2)
Cohort 4			12 mg/kg VIS649 (N=7)	Placebo (N=2)
Optional Cohort 5			Up to but not greater than 20 mg/kg VIS649 (N=7)	Placebo (N=2)

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]

No more than one Japanese subject per cohort may be randomized to receive placebo.

5.6. Administration of Investigational Medicinal Products

The amount of VIS649 will be calculated on a per subject weight basis and administered diluted in 100 mL of 0.9 % sodium chloride. VIS649 will be administered intravenously using a volumetric pump and through a 0.22µm in line IV filter at a rate of 100 mL/hr over the course of one hour. A saline flush is performed after the infusion is complete to ensure that any drug product remaining in the infusion line is administered. Placebo will be 100 mL of 0.9% sodium chloride administered IV in an identical manner. Refer to the pharmacy manual for specific details on storage, handling, and preparation information.

5.7. Compliance

Dosing will be performed by trained, qualified personnel designated by the Principal Investigator. The date, time and volume of the administered dose will be documented. Comments will be recorded if there are any deviations from the planned dosing procedures.

5.8. Blinding and Breaking the Blind

The clinical study will be performed in a double-blind manner, for clinical research unit staff interacting with study participants, with the exception of the persons involved in the preparation of the IMPs. These persons will not be involved in any other study activities.

Prior to scheduled unblinding as described below, the study blind should not be broken except in a medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency). The decision to break the blind will be made on a case-by-case basis, at the discretion of the Principal Investigator in collaboration with the Sponsor/Medical Monitor. The applicable Standard operating procedure (SOP) will be followed for blind breaking procedures.

As participants in each dosing cohort complete their Week 16 visit, data clean-up and soft-lock will be performed for each cohort, to allow interim assessments of blinded data. PK/PD analysts will have access to unblinded data at all times, but those individuals will not be involved in study participant interactions. Summaries of treatment specific PD responses (principally, individual immunoglobulin levels over time and group mean, median, minimum and maximum parameters by treatment assignments) will be prepared and shared with the Sponsor, in a manner that does not unblind individual patient treatment assignments. A registry of dummy subject identifiers will be created. A physician who is not involved in the study will review Ig results to maintain the blind for the Principal Investigator.

5.9. Prior and Concomitant Medications

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. Prior and concomitant medication use is not permitted from last 30 days or five half-lives, whichever is longer, preceding Baseline (Day -1) until end-of-study (including prescription or non-prescription [over-the-counter]) medication, except, acetaminophen or ibuprofen, hormonal contraceptives, topical medications, vitamins, dietary or herbal). However, concomitant medication use may be warranted for the treatment of AEs. The use of concomitant medications to treat AEs should be discussed between the Principal Investigator and the Medical Monitor.

5.10. Treatment of Overdose

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

6. MEASUREMENTS AND METHODS OF ASSESSMENT

For timing of assessments, refer to the Schedule of Assessments Table 9.

A Safety Management Plan will be signed between the Sponsor and PAREXEL.

6.1. Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Medication history
- Reproductive history

The following demographic information will be recorded:

- Age
- Ethnic origin: Hispanic/Latino or not Hispanic/not Latino
- Race: White, American Indian/Alaska Native, Japanese, Asian (non-Japanese), Native Hawaiian or other Pacific Islander, Black/African American
- Height, without shoes (cm)
- Body weight, without shoes (kg)
- BMI (kg/m^2)

Other Baseline characteristics will be recorded as follows:

- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- History of blood or plasma donation

6.2. Safety Variables

6.2.1. Adverse Events

Adverse event reporting will begin for each subject from Baseline (Day -1) and will continue until the End-of-study Visit.

6.2.1.1. Definitions

6.2.1.1.1. Definition of Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g. those occurring during treatment-free periods (including post-dosing periods), in association with study-related procedures and assessments, or under placebo. For study drugs, lack of efficacy may be an expected potential outcome and should not be reported as an AE unless the event is unusual in some way, e.g., greater in severity.

Concomitant illnesses, which existed prior to entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as part of the subject's medical history.

6.2.1.1.2. Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening; this means that the subject was at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires in-patient hospitalization or prolongation in existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is another important medical event (see below)

Important medical events that do not result in death, are not life-threatening or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or in a physician's office, blood dyscrasias or seizures

that do not result in in-patient hospitalization, and the development of drug dependency or drug abuse.

A distinction should be drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes would be considered an SAE, but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but would not be considered an SAE.

Medical and scientific judgment should be exercised in deciding if an AE is serious and if expedited reporting is appropriate.

6.2.1.1.3. Adverse Events of Special Interest

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Principal Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor to other parties might also be warranted.

Examples of these are all AEs of

- Infusion reactions: Fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, and chest pain
- Delayed allergic reactions: Serum sickness (i.e., urticaria, fever, general glandular enlargement, joint pains)
- General: Injection site reaction
- Any documented infection

6.2.1.2. Recording of Adverse Events

Adverse events should be collected and recorded for each subject from the Baseline (Day -1) until the end of their participation in the study, i.e. the subject has discontinued or completed the study.

Adverse events may be volunteered spontaneously by the subject, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as 'How have you been feeling since you were last asked?' All AEs and any required remedial action will be

recorded. The nature of AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity and action taken of the AE will be documented together with the Principal Investigator's assessment of the seriousness of the AE and causal relationship to study drug and/or study procedure.

All AEs should be recorded individually in the subject's own words (verbatim) unless, in the opinion of the Principal Investigator, the AEs constitute components of a recognized condition, disease or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AEs will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.0 or higher).

6.2.1.3. Assessment of Adverse Events

Each AE will be assessed by the Principal Investigator with regard to the categories discussed in the following sections.

6.2.1.3.1. Intensity

The Principal Investigator will assess all AEs for severity in accordance with the following standard ratings.

- Mild: Ordinarily transient symptoms, does not influence performance of subject's daily activities. Treatment is not ordinarily indicated.
- Moderate: Marked symptoms, sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Treatment may be necessary.
- Severe: Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue in the study and treatment may be necessary.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted for that day. Any change in severity of signs and symptoms over a number of days will be captured by recording a new AE, with the amended severity grade, and the date (and time, if known) of the change.

6.2.1.3.2. Causality

The Principal Investigator will assess the causality/relationship between the study drug and the AE. One of the categories described in Table 6 should be selected based on medical judgment, considering the definitions below and all contributing factors.

Table 6 Assessment of Relationship of Adverse Events to Investigational Product

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (de-challenge*) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge† procedure if necessary.
Probably related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
Possibly related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
Unlikely to be related	A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative de-challenge and re-challenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors or other drugs or chemicals).

*De-challenge is when a drug suspected of causing an AE is discontinued. If the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, this is termed a positive de-challenge. If the symptoms continue despite withdrawal of the drug, this is termed a negative de-challenge. Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

†Re-challenge is when a drug suspected of causing an AE in a specific subject in the past is re-administered to that subject. If the AE recurs upon exposure, this is termed a positive re-challenge. If the AE does not recur, this is termed a negative re-challenge.

6.2.1.3.3. Seriousness

Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2.1.1.2.

6.2.1.4. Reporting of Serious Adverse Events

The Principal Investigator will review each SAE and evaluate the intensity and the causal relationship of the event to study drug. All SAEs will be recorded from signing of the ICD until the End-of-study Visit. Serious AEs occurring after the End-of-study Visit and coming to the attention of the Principal Investigator must be reported only if there is (in the opinion of the Principal Investigator) reasonable causal relationship with the study drug.

The Principal Investigator is responsible for providing notification to the Clinical Research Organization (CRO)/Sponsor of any SAE, whether deemed IMP-related or not, that a subject experiences during their participation in study within 24 hours of becoming aware of the event.

As a minimum requirement, the initial notification should provide the following information:

- Study number
- Patient number
- Sex
- Date of birth
- Name of Principal Investigator and full clinical site address
- Details of SAE
- Criterion for classification as 'serious'
- Study drug name, or code if unblinded, and treatment start date
- Date of SAE onset
- Causality assessment (if sufficient information is available to make this classification)

The CRO/Sponsor will request clarification of omitted or discrepant information from the initial notification. The Principal Investigator or an authorized delegate is responsible for emailing or faxing the requested information to the CRO/Sponsor within 24 hours of the request.

Initial reports of SAEs must be followed later with detailed descriptions, including clear photocopies of other documents as necessary (e.g. hospital reports, consultant reports, autopsy reports), with the subject's personal identifiers removed. All relevant information obtained by the Principal Investigator through review of these documents will be recorded and faxed to the Sponsor within 24 hours of receipt of the information. If a new SAE Report Form is faxed, then the Principal Investigator must sign and date the form. The CRO/Sponsor may also request additional information on the SAE, which the Principal Investigator or an authorized delegate must fax to the Sponsor within 24 hours of the request.

Serious Adverse Event Reporting:

PAREXEL Safety Services

[redacted]

[redacted]

[redacted]

6.2.1.5. Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to Baseline or stabilized at a level acceptable to the Principal Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed or until the subject is lost to follow-up.

6.2.1.6. Pregnancy

The Sponsor has a responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be regarded as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Each pregnancy must be reported by the Principal Investigator to the Sponsor within 24 hours after becoming aware of the pregnancy. The Principal Investigator must follow-up and document the course and the outcome of all pregnancies even if the subject was withdrawn from the clinical study or if the clinical study has finished.

All outcomes of pregnancy must be reported by the Principal Investigator to the Sponsor on the pregnancy outcome report form within 24 to 48 hours after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

6.2.2. Clinical Laboratory Assessments

Samples for clinical laboratory assessments will be collected at the time points detailed in the Schedule of Assessments Table 9. Clinical laboratory tests will be performed by the laboratories mentioned in the List of Study Staff of this clinical study protocol. Samples will be collected in appropriate tubes and handled according to standard procedures of the applicable laboratory.

Table 7 lists the biochemistry, hematology and urinalysis tests that will be performed by the local laboratory for safety blood samples.

Table 7 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)	
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)	

Abnormal laboratory results should be recorded as AEs (e.g., Principal Investigator judgment or outside the specific reference range).

Any value outside the normal range will be flagged for the attention of the Principal Investigator or designee at the site. The Principal Investigator or designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during the Screening period is indicated as clinically significant, the subject will not be allowed into the study without permission of the Medical Monitor. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the End-of-study Visit, it should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized, at the discretion of the Principal Investigator.

6.2.2.1. Anti-drug Antibody Response

The serum samples to measure the presence of ADA will be collected on Days 1, Week 4,8,16 and if required Weeks 20 and 24. The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Blood samples for ADA analysis will be collected up to Week 16 from all subjects. Samples for anti-VIS649 antibody titers and neutralizing capabilities will be drawn according to the Schedule of Assessments Table 9. Further procedures for sample collection, shipment, processing and storage will be described in the Laboratory Manual.

6.2.3. Vital Signs

Vital signs will be assessed at the time points detailed in the Schedule of Assessments Table 9. The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Pulse (bpm)
- Respiratory rate (breaths per minute)
- Temperature

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

6.2.4. Standard 12-lead Electrocardiograms

Standard safety 12-lead ECGs will be performed at the time points detailed in the Schedule of Assessments Table 9.

The12-lead ECGs will be performed after the subject has been resting supine for≥ 5 minutes. The ECG will include all 12 standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected: PR interval, QRS interval, RR interval, QT interval and QTc interval (QTcB or QTcF).

All ECGs must be evaluated by a qualified physician for the presence of abnormalities.

6.2.5. Physical Examinations

Physical examinations will be performed at the time points detailed in the Schedule of Assessments Table 9.

Full physical examination:

An assessment of general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic and psychiatric systems).

Brief physical examination:

An assessment of the general appearance, skin, cardiovascular system, respiratory system and abdomen.

The brief physical examination may be extended to a full physical examination if considered necessary by the Principal Investigator. Other evaluations may be performed as deemed necessary by the Principal Investigator. This will be commented upon in the clinical study report (CSR), if performed.

6.3. Pharmacokinetics Variables

6.3.1. Blood Sample Collection

Blood for the analysis of VIS649 will be collected at the time points detailed in the Schedule of Assessments Table 9.

Blood sample collection, processing and shipping details will be outlined in a separate laboratory manual. In brief, PK sampling will occur on Day 1 starting with a collection 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. Pharmacokinetics samples will also be drawn on Days 3, 7, 14, 28, 42, 56, 70, and 112 days. Serum samples for determination of the concentration of VIS649 will be analyzed under the responsibility of the Sponsor. Further procedures for sample collection, shipment, processing, and storage will be described in the Laboratory Manual.

6.4. Pharmacodynamics Variables

For assessing the effect of VIS649 on PD parameters, serum samples will be drawn and evaluated for immunoglobulin levels (total IgA, IgG and IgM), immunoglobulin subtypes (IgA and IgG), and lymphocytes. [redacted]. Samples for PD parameters will be collected at the time points detailed in the Schedule of Assessments Table 9. Further procedures for sample collection, shipment, processing, and storage will be described in the Laboratory Manual.

6.5. Total Amount of Blood

The approximate volume of blood (327 mL) planned for collection from each subject over the course of the entire study (from the Screening Visit to the End-of-study Visit, but not including repeat or additional tests ordered by the Principal Investigator) presents no undue risk to the subjects.

For all subjects enrolled, the approximate blood volumes to be collected during the study are outlined in Table 8.

Table 8 Approximate Total Amount of Blood for Each Subject

Assessment	Sample Volume (mL)	Number of Samples	Total Blood Volume (mL)
Pharmacokinetics			
VIS649	5	13	65
Pharmacodynamics			
Ig	3	17	51
Ig subtypes	5	6	30
Lymphocytes	4	8	32
[redacted]	[redacted]	[redacted]	[redacted]
ADA	5	4	20
Clinical laboratory tests			
Hematology	4	7	28
Clinical chemistry[1]	8.5	4	34
Coagulation[2]	4.5 (+1)	4	22
Total Blood Volume[3] per Subject			327

Abbreviations: ADA: Anti-drug Antibody; Ig: Immunoglobulin; PD: Pharmacodynamics

[1]Viral serology and pregnancy tests (women of childbearing potential only) will be performed on the sample collected for clinical chemistry at the Screening Visit.

[2] Additional 1mL of blood is collected as a discard tube prior to sample collection.

[3] Includes 2 additional follow-up laboratory visits, if needed, per Table 9. Total does exclude repeat and additional laboratory investigations

7. STUDY CONDUCT

7.1. Schedule of Assessments

The study will be comprised of:

- A Screening Visit up to 28 days before dosing
- An in-house stay for approximately 2 to 3 days, with admission to the study center on Day -1, dosing on Day 1 and discharge in the morning of Day 2
- A post-administration period of 16 weeks
- Outpatient visits, on Day 3 (+1 day), 7 (± 1 day), 14, 21, 28, 35, 42, 49, 56, 70, 84 and 98 (all visits± 3 days)
- A final Follow-up visit on Day 112 (± 3 days); however, two additional follow-up visits may be performed, at Weeks 20 and 24 post-dosing, if serum immunoglobulins have not returned to > lower limits of normal by the Week 16 (Day 112) visit or if emerging trial data suggest a value of later follow-up (i.e. detection of ADA responses).

The total duration of the clinical study per subject will be up to approximately 20 weeks (5 months), including the Screening period with the possibility of duration extending to 28 weeks (7 months) if follow-ups visits are required. For details of Schedule of Assessments, please see: Table 9.

Table 9 Schedule of Assessments

Activity	Screen	Baseline	Post-Dosing Period Assessments															Additional Visits[7]	
Time Point (Day)	**Days -30 to -1**	**BL D-1 pre-dose**	**D1**	**D2**	**D3**	**W1/ D7**	**W2/ D14**	**W3/ D21**	**W4/ D28**	**W5/ D35**	**W6/ D42**	**W7/ D49**	**W8/ D56**	**W10/ D70**	**W12/ D84**	**W14/ D98**	**W16/ D112**	**W20**	**W24**
+/- visit allowance	**N/A**	**N/A**	**N/A**	**N/A**	**+1**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-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[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 Examination - Brief					x				x				x		x		x		

Activity	Screen	Baseline	Post-Dosing Period Assessments															Additional Visits[7]	
Time Point (Day)	**Days -30 to -1**	**BL D-1 pre-dose**	**D1**	**D2**	**D3**	**W1/ D7**	**W2/ D14**	**W3/ D21**	**W4/ D28**	**W5/ D35**	**W6/ D42**	**W7/ D49**	**W8/ D56**	**W10/ D70**	**W12/ D84**	**W14/ D98**	**W16/ D112**	**W20**	**W24**
+/- visit allowance	**N/A**	**N/A**	**N/A**	**N/A**	**+1**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-5**	**+/-5**
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	x
AE Check		x	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		x		x	x			x		
Blood Sampling for PD (Immunoglobulins)	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood Sampling for Ig subtypes		x				x			x				x		x		x		
Blood Sampling for PD (lymphocyte populations)		x				x			x				x		x		x	x	x

Activity	Screen	Baseline	Post-Dosing Period Assessments															Additional Visits[7]	
Time Point (Day)	**Days -30 to -1**	**BL D-1 pre-dose**	**D1**	**D2**	**D3**	**W1/ D7**	**W2/ D14**	**W3/ D21**	**W4/ D28**	**W5/ D35**	**W6/ D42**	**W7/ D49**	**W8/ D56**	**W10/ D70**	**W12/ D84**	**W14/ D98**	**W16/ D112**	**W20**	**W24**
+/- visit allowance	**N/A**	**N/A**	**N/A**	**N/A**	**+1**	**+/-1**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-3**	**+/-5**	**+/-5**
[redacted]																			
Blood sampling for ADA		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.
3. Vitals signs at Screening 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. Vital signs at other timepoints will be limited to 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.

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 (Day 112).
6. [redacted]
7. Follow-up visits may be performed if serum immunoglobulin levels or lymphocytes have not returned to > lower limits of normal or if emerging trial data suggest a value of later follow-up (i.e. for ADA responses)

7.2. Order of Assessments

The following priority order will be in effect when more than one assessment is required at a pre-dose and post-dose time point, with PK blood sampling being performed nearest to the specified time:

1. 12-lead ECG
2. Vital signs
3. PK blood sampling
4. Blood sampling for safety assessments

7.3. Early Termination

If a subject withdraws prematurely after dosing, all data normally collected at discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge. If deemed necessary by the Principal Investigator, the subject will be asked to return at the regularly scheduled End-of-study Visit.

7.4. End-of-Study

End-of-study is defined as completion of the final follow-up visit. For those subjects that withdraw prematurely, end-of-study is defined as the time of the subject's last data collection.

7.5. Restrictions

7.5.1. Dietary and Fluid Restrictions

Nicotine: Nicotine-containing products (including but not limited to cigarettes, cigars, and chewing or dipping tobacco) is prohibited within less than 3 months before study drug administration. Use of topical or oral nicotine preparations for smoking cessation is also prohibited within less than the past 90 days before study drug administration. Included subjects must abstain from consumption of nicotine-containing products for the duration of the study.

Caffeine: Consumption of greater than 500 mg of caffeine or xanthine-containing products per day (e.g., coffee, tea, soft drinks, energy drinks, or chocolate) is prohibited. Included subjects must abstain from consuming caffeine or xanthine-containing products from 48 hours prior to check-in on Day -1 through the end of the study.

Alcohol: Consumption of more than 21 units of alcohol (1 unit of alcohol is equivalent to 8 ounces of beer, 4 ounces of wine, or one ounce of spirits) per week (7 days) is prohibited. Included subjects must abstain from consuming alcohol from 48 hours prior to check-in on Day -1 through the end of the study.

Grapefruit: Consumption of grapefruit foods or beverages, or Seville-orange containing foods (e.g., orange marmalade) or beverages is prohibited from 48 hours prior to check-in on Day -1 through the end of the study.

7.5.2. Other Restrictions

Medications: Use of prescription or non-prescription (OTC) except acetaminophen or ibuprofen, hormonal contraceptives, topical medications, vitamins, dietary or herbal supplements is prohibited during the last 30 days or five half-lives, whichever is longer, preceding Baseline (Day -1) is prohibited. Concomitant use of marketed or investigational systemic immunosuppressive or immunomodulatory medications (e.g., corticosteroids, methotrexate, azathioprine, etc. and/or biologics) is prohibited during the last 30 days or five half-lives, whichever is longer.

Other: Blood donation (>500 mL) within 60 days prior to start of Screening and/or donation of any plasma within 7 days prior to Baseline (Day -1) and for the duration of the study is prohibited.

8. STATISTICAL METHODS

Before database lock, a statistical analysis plan will be issued as a separate document, providing detailed methods for the analyses outlined below. Any deviations from the planned analyses will be described and justified in the CSR.

8.1. Determination of 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.

8.2. Study Population

8.2.1. Disposition of Subjects

Subjects entering and completing the clinical study will be listed and summarized using number and percentage

Subjects excluded from the safety, PK and PD analysis sets and data excluded from the PK and PD analysis sets will be listed including the reason for exclusion. Subject disposition will be summarized. Disposition data will be presented based on all subjects randomized.

8.2.2. Protocol Deviations

Protocol deviations will be listed by subject.

8.2.3. Analysis Populations

- 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.
- 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.
- ADA Evaluable Population: The PK population subset with ADA assessment post study drug (VIS649 or placebo) dosing. Subjects will be included in the analysis according to the dose and study drug received.

- PD population: The PK 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.

8.3. General Considerations

In general, descriptive statistics for continuous variables will be summarized by treatment group using number of subjects, arithmetic mean, standard deviation, median, minimum and maximum; descriptive statistics for categorical data will be summarized by treatment group using frequency counts and percentages. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, standard deviation, arithmetic %CV, and geometric mean, median, geometric %CV, minimum and maximum.

The placebo subjects from all cohorts will be pooled into a single placebo group for all summaries and presentations.

8.4. Demographic and Anthropometric Information and Baseline Characteristics

Demographic and anthropometric variables (age, sex, ethnicity, race, height, weight and BMI) will be listed by subject. Demographic characteristics (age, sex, ethnicity and race) and anthropometric characteristics (height, weight and BMI) will be summarized by treatment and for all subjects in the safety population. The denominator for percentages will be the number of subjects in the safety population for each treatment or for all subjects as applicable.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA System Organ Class (SOC), MedDRA Preferred Term (PT), start date, and stop date (or ongoing if applicable).

8.5. Prior and Concomitant Medication

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

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

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

8.6. Drug Administration

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

8.7. Safety Analyses

8.7.1. Adverse Events

Adverse events will be coded using the MedDRA version 21.0 or higher. All AEs will be listed. The incidence of treatment-emergent AEs will be summarized by SOC and PT for each treatment and overall, by severity, and by relationship to IMP.

The categories of the relationship to IMP will be summarized as related (Related, Probably related, and Possibly related) and not related (Unlikely to be related and Unrelated).

Serious AEs will be listed.

Injection site tolerability is defined as AEs demonstrating significant injection site irritation or tissue damage. Injection site tolerability will be reported by treatment group, and time point.

8.7.2. Clinical Laboratory Tests

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

Clinical laboratory tests (observed values) will be summarized descriptively in tabular format. Shift tables will be presented for select laboratory parameters.

8.7.3. Vital Signs

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

Observed values as well as change from baseline data will be summarized descriptively in tabular format.

8.7.4. Standard 12-lead Electrocardiogram

Standard 12-lead ECG data (observed and change from baseline) will be listed for each subject and time point. Observed values will be classified using frequency counts for normal, abnormality that is not clinically significant, and clinically significant abnormality by dose cohort and time point of collection. Descriptive statistics will be calculated for ECG parameters. The incidence of abnormalities, based on the clinical interpretations from the Investigator, will be enumerated by cohort, and visit. Categorical change from baseline will be summarized descriptively for QTc data.

8.7.5. Physical Examination

Abnormal physical examination findings will be listed.

8.8. Pharmacokinetics Analyses

VIS649 serum concentrations will be listed by subject. Two sets of summary statistics of VIS649 serum concentrations will be presented by cohort; the first will combine the races and the second set will stratify each cohort by race group. Individual and mean VIS649 concentration-time profiles will be plotted for each cohort in both linear and logarithmic scales. Pharmacokinetics parameters will be summarized by cohort for Japanese and non-Japanese subjects using descriptive statistics. [redacted]

Pharmacokinetics and/or PK/PD modeling may be used for further characterization of data and will be reported separately.

8.9. Pharmacodynamics Analyses

Pharmacodynamic analysis will be performed using data from all subjects assigned to the PD Population.

PD for circulating lymphocyte, total IgA, IgG and IgM, and other relevant PD applicable markers in serum or appropriate matrix (using the raw data, change from baseline data and % change from baseline, as appropriate) will be summarized and plotted over time. Baseline data will be taken as the last measurement prior to dosing or average of the Screening and Baseline values, detail will be written in Statistical Analysis Plan.

8.10. Pharmacokinetics/Pharmacodynamics Analyses

[redacted]

8.11. Immunogenicity Data (Antibody to VIS649)

Anti-VIS649 ADA evaluations will be listed including the confirmatory assay (positive/negative). A summary table of the ADA response (positive or negative) will be presented, by treatment (dose of VIS649 or pooled placebo), based on the safety analysis set. In addition, the ADA titers (n, median, minimum and maximum) will be summarized by treatment (dose of VIS649 or pooled placebo) for all subjects with a positive confirmatory assay at each time point; this tabulation will include a summary of the highest titer across all time points for each subject. [redacted]

8.12. Interim Data Reviews

As participants in each dosing cohort 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, 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 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.

9. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

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

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

All aspects of the study will be carefully monitored with respect to Good Clinical Practice (GCP) and SOPs for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator. The Sponsor will be entitled to audit the facilities used in the clinical and laboratory parts of the study, as well as to access all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of the a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory/ethics agency concerning an inspection.

9.2. Institutional Review Board

Before implementing this study, the protocol, the proposed ICF and HIPAA authorization, and other information given to study volunteers must be reviewed by the IRB of the study site. A signed and dated statement that the protocol and ICF and HIPAA authorization have been approved by the IRB must be given to the Sponsor before study initiation. The name and occupation of the chairperson and the members of the IRB or the IRB's Health and Human Services (assurance number must be supplied to the Sponsor.

9.3. Access to Source Data/Documents

PAREXEL will use an electronic data capture system to manage data collection during this trial. The electronic data capture system (ClinBase) is a software tool designed to ensure quality

assurance and facilitate data capture during clinical trials. Through a system regulated workflow that includes barcode scanning and interfaces to medical equipment to avoid manual data entry, study operations performance is controlled and captured in real time. The system is fully CFR 21 part 11 compliant.

The Principal Investigator will ensure the accuracy, completeness and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability and consistency. A complete audit trail will be maintained of all data changes. The Principal Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Principal Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each subject receiving study drug.

The Principal Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors and the IRB/IEC to have direct access to all documents pertaining to the study.

9.4. Archiving Study Documents

According to ICH SOP guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.5. Good Clinical Practice

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Principal Investigator abide by the principles of the ICH guidelines on GCP. The clinical study also will be carried out in keeping with national and local legal requirements in accordance with US investigational new drug [IND] regulations [21 CFR 56]).

9.6. Informed Consent

Before each subject is enrolled in the clinical study, written informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country. As part of this procedure, the Principal Investigator must explain orally and in writing the nature, duration and purpose of the study and the action of the drug in such a manner that the subject is aware of the potential risks, inconveniences or AEs that may occur. The subject should be informed that he/she is free to withdraw from the study at any time. He/She will receive all information that is required by federal regulations and ICH guidelines. The Principal Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICD prior to the start of the study.

The ICD must be signed and dated; one copy will be handed to the subject, and the Principal Investigator will retain a copy as part of the clinical study records. The Principal Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICD may need to be revised to reflect the changes to the protocol. If the ICD is revised, it must be reviewed and approved by the responsible IRB/IEC, and signed by all subjects subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.7. Protocol Approval and Amendment(s)

Before the start of the clinical study, the clinical study protocol and other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the clinical study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, which must be released by the responsible staff and receive IRB/IEC approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment, but will also be mentioned in the integrated CSR. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

All protocol deviations will be documented and reported in the final CSR.

9.8. Confidentiality Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs and other material) will be stored appropriately to ensure their confidentiality. The Principal Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial or to comply with regulatory requirements.

The anonymity of participating subjects must be maintained. Subjects will be specified on study documents by their subject number, initial or birth date, not by name. Documents that identify the subject (e.g., the signed ICD) must be maintained in confidence by the Principal Investigator.

9.9. Publication Policy

By signing the clinical study protocol, the Principal Investigator agrees with the use of results of the clinical study by the Sponsor for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the regulatory authorities will be notified of the Principal Investigator's name, address, qualifications and extent of involvement.

A Principal Investigator shall not publish any data (poster, abstract, paper, etc.) without the express written consent of the Sponsor.

10. REFERENCE LIST

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