Official Title: **Protocol VIS410-202, A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection**

NCT Number: **NCT02989194**

Document Date: **14 March 2017**

[redacted] [redacted]

Visterra

Clinical Study Protocol

A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection

Product	VIS410
Protocol Number	VIS410-202
EudraCT Number	2015-004546-26
Clinical Phase	2a
Clinical Indication	Influenza infection
Issue Date (Version)	14 March 2017 (Version 2.2)

Sponsor	Visterra, Inc. One Kendall Square, Suite B3301 Cambridge, MA 02139 United States of America
Sponsor Representative	[redacted]

[redacted]

SIGNATURES

Signature of Sponsor Representative

Title: A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection

Name: José Trevejo, MD, PhD

'This Clinical Study Protocol has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practice.'

Signature:

Date: 14 MAR 2017

Signature of Investigator

Title: A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection

Name:

Affiliation:

Address:

'I have read and understood all sections of the protocol entitled, "A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection."

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol, the International Conference on Harmonisation tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Visterra, Inc., or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational product to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Visterra, Inc.'

Signature:

Date:

PROTOCOL HISTORY

Protocol History Visterra, Inc. – VIS410-202			
Document	**Issue Date**	**Amendment Type**	**Comments**
Initial Clinical Study Protocol	6 January 2016	-	This document
Revised Clinical Study Protocol	14 September 2016		
Revised Clinical Study Protocol	12 October 2016	Country Specific-South Africa	Inclusion of HIV testing at baseline
Revised Clinical Study Protocol	14 March 2014	Country Specific South Africa	Modification of HIV exclusion criteria #12

TABLE OF CONTENTS

List of Tables

List of Figures

SYNOPSIS

Name of Company: Visterra, Inc.		(for national authority only)
Name of the Finished Product:	Not applicable	
Name of the Active Substance:	VIS410	
Study Title:	**A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection**	
Protocol Number	VIS410-202	
EudraCT Number	2015-004546-26	
Clinical Indication:	Influenza infection	
Clinical Phase:	2a	
Number of Clinical Sites:	Approximately 50-75 sites worldwide	
Number of Subjects:	Approximately 150	

Objectives:

Primary Objective:

- Assess the safety and tolerability of a single intravenous (IV) dose of VIS410 in patients with uncomplicated influenza infection

Secondary Objectives:

- Evaluate the efficacy of VIS410 compared with placebo on the time to alleviation of clinical symptoms of acute uncomplicated influenza
- Evaluate the effect of VIS410 on severity of influenza infection
- Assess the pharmacokinetics of VIS410 in serum
- Assess the effects of VIS410 on viral shedding
- Assess the immunogenicity of VIS410

Exploratory Objectives:

- Assess the pharmacokinetics of VIS410 from nasopharyngeal secretions
- Assess viral isolates to determine the emergence of VIS410-resistant viruses
- Assess correlations between virology, safety, pharmacokinetics, viral shedding, clinical symptoms, and other endpoints
- Assess the anti-influenza immune response

Study Design:

This is a Phase 2a randomized, double-blind, placebo-controlled study to be conducted in approximately 150 subjects with uncomplicated influenza. Subjects will be admitted to an infusion unit for drug administration and observation following infusion. The study is designed to compare an infusion of a single high or low IV dose of VIS410 against placebo. Subjects will be assigned randomly to receive VIS410 at a dose of 2000 mg (low dose) or 4000 mg (high dose) or placebo (0.9% sodium chloride) at a ratio of 1:1:1 using a permuted block randomization method. Eligible subjects will receive VIS410 2000 mg, VIS410 4000 mg, or placebo administered as a single IV infusion over 2 hours on Day 1. Subjects will receive a pretreatment regimen of diphenhydramine 50 mg PO and ibuprofen 400 mg PO or acetylsalicylic acid 325 mg PO 60 minutes before infusion.

The subjects will be observed for at least 2 hours after the end of the infusion and will have a follow-up phone

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call in the evening of the dosing day to ensure subjects' safety and well-being. Subjects will return for follow-up visits on Days 3 (±1 day), 5 (±1 day), 7 (±1 day), 14 (±3 days), 28 (±3 days), 56 (±7 days) and 100 (±7 days). In addition, between clinic visits up to Day 7 (e.g., on Days 2, 4 and 6) subjects will receive a follow-up telephone call to ensure compliance with FluPRO Influenza Symptom Questionnaire and review any new or worsening signs or symptoms.

The Schedule of Assessments is presented in Table 1.

In case of clinical worsening of influenza-related symptoms recorded at baseline or development of two new symptoms after 48 hours of study drug administration, additional antiviral prescription medication may be used, at the discretion of the Investigator, for management of influenza-like symptoms per standard of care. The use of over-the-counter, symptom-modifying drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, or pseudoephedrine are discouraged and paracetamol/acetaminophen should be encouraged as a replacement medication.

In case of hospitalization due to worsening of influenza symptoms, subjects should be managed per standard of care and local guidelines, which may include use of neuraminidase inhibitors. An independent Data Safety Monitoring Board (DSMB) will be established to review all available safety data after 30 subjects have completed the Day 5 visit and again after 75 subjects have completed the Day 28 visit. In addition, following the first DSMB, the DSMB will convene if the overall relative gastrointestinal (GI) adverse event rate reaches 50% or the rate of moderate GI adverse events reaches 25%. Study enrollment and dosing will continue whilst the DSMB evaluates data.

Based upon any safety assessments and after mutual agreement with the Investigator (or designee) and the Sponsor, the study may be temporarily or permanently halted.

Dosing will temporarily pause whilst the DSMB meets if:

- a drug-related or unexpected drug-related SAE occurs in at least 1 subject
- 25% or more subjects have GI symptoms of Grade 3 following the first DSMB.

Doses may be adjusted downward at the discretion of the DSMB based on review of safety data including GI adverse events.

Study Population:

Approximately one hundred fifty (150) subjects will be enrolled in 3 equal arms: VIS410 2000 mg, VIS410 4000 mg, and placebo. The subjects will be carefully screened for eligibility.

Inclusion Criteria:

Subjects meeting all of the following criteria are eligible to participate in this study:

1. Male and female subjects aged ≥18 years and <65 years
2. Women should fulfill one of the following criteria:
    a. Post-menopausal; either amenorrhea ≥12 months or follicle stimulating hormone >40 mIU/mL as documented in their medical history.
    b. Surgically sterile; hysterectomy, bilateral oophorectomy, or tubal ligation.
    c. Women of childbearing potential participating in heterosexual sexual relations must be willing to use adequate contraception from screening until 60 days post-infusion, per Section 7.1.2.
3. Non-vasectomized (or vasectomized less than 6 months prior to dosing) male subjects who have a female partner of childbearing potential must use an effective birth control method (see Section 7.1.2) when having heterosexual intercourse, from screening until 60 days post-infusion.
4. Test positive for influenza A by Rapid Antigen Test performed with a commercially available test on an adequate nasopharyngeal specimen in accordance with the manufacturer's instructions
5. Presence of at least one respiratory symptom (cough, sore throat, or nasal symptoms) of moderate to severe intensity, or presence of at least one constitutional symptom (myalgia [aches and pains], headache, feverishness, or fatigue) of moderate to severe intensity
6. Onset of symptoms (time when the temperature was first measured as elevated [temperature of ≥100.4°F or ≥38°C], OR the time when the subject experienced at least one respiratory symptom or at

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least one constitutional symptom) no more than 72 hours before the start of infusion
7. Subject is able and willing to comply with study procedures, as per protocol
8. Subject is able and willing to give voluntary written informed consent

Exclusion Criteria:

Subjects meeting any of the following criteria are excluded from participation in this study:

1. Use of NSAIDs or antihistamines within 6 hours of study drug dosing with the exception of those used as part of the pretreatment regimen.
2. History of intolerance or allergic response to monoclonal antibodies and/or pretreatment medications diphenhydramine, ibuprofen and acetylsalicylic acid)
3. History of receiving monoclonal antibody products within 3 months prior to enrollment in this study or planned administration during the study period
4. Subjects in whom nasopharyngeal swabbing is not possible
5. Subject weight less than (<) 45 kg
6. Subjects with clinical history that would lead to increased risk of influenza complications including but not limited to clinically significant cardiac disease, moderate to severe asthma, or other moderate to severe chronic obstructive pulmonary disease, metabolic syndrome including moderate to severe diabetes or active tuberculosis.
7. History of chronic GI disease, including bleeding, ulceration, Irritable Bowel Syndrome, systemic mastocytosis or chronic diarrhea
8. Women who are pregnant, breast-feeding, or considering becoming pregnant.
9. Patients with hypoxemia requiring oxygen support.
10. Clinical evidence of worsening of any chronic medical condition (temporally associated with the onset of symptoms of influenza) which, in the Investigator's opinion, indicates that such finding(s) could represent complications of influenza
11. Presence of immunocompromised status due to chronic illness, previous organ transplant, or use of immunosuppressive medical therapy including systemic steroids.
12. Presence of known human immunodeficiency virus (HIV) infection PLUS any one of the following:
    a. A CD4 count ≤500 cells/mm^3 (CD4 count obtained within the 3 months prior to screening)
    b. An Acquired Immune Deficiency Syndrome-defining illness. (HIV testing required at screening visit for all patients with no documented HIV status within 3 months prior to screening.)
13. Presence of known chronic hepatitis B or hepatitis C.
14. Receipt of any dose of antiviral therapy such as, but not limited to, rimantadine, amantadine, peramivir, zanamivir, laninamivir or oseltamivir in the 7 days prior to screening
15. Enrollment in any other investigational drug or device study, any disease or vaccine study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer
16. Presence of any pre-existing illness that, in the opinion of the Investigator, would place the subject at an unreasonably increased risk through participation in this study
17. Subjects unable to comply with study protocol procedures and study visit schedules for whatever reason
18. Subjects unable to take oral predose medication
19. Known or suspected alcohol or drug abuse, that is, abuse of a level that would compromise the safety or cooperation of the subject in the opinion of the Investigator
20. Subjects on chronic medications where the dose has not been stable for at least 3 months

Test Product, Dose, Mode of Administration:

VIS410 (2000 mg or 4000 mg) will be administered IV over 2 hours as a single 200-mL infusion followed by a 25 mL saline flush to ensure all product is administered.

Reference Product, Dose, Mode of Administration:

Placebo, normal saline solution (0.9%), will be administered IV over 2 hours as a single 200-mL infusion

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followed by a 25 mL saline flush to ensure all product is administered.

Study Drug Preparation:

The required amount of VIS410 to be dosed (2000 mg or 4000 mg) will be diluted with normal saline up to a total volume of 200 mL; for placebo subjects, 200 mL of normal saline will be prepared. Length of IV line will be set for max volume of 25 mL so that the 25 mL saline flush following administration will ensure all study product has been administered.

The study infusion will be administered IV using a 0.22 µm in-line filter and will be controlled by a volumetric pump. Standard, uniform-length infusion lines will be used and microfilters will be provided by the Sponsor.

The infusion bag will be covered with an opaque sleeve in the pharmacy to maintain the study blind. The study drug will be administered IV at a rate of 100 mL/h, over 2 hours. After 200 mL of the diluted dose has been administered, the infusion will be stopped; followed by a 25-mL saline flush. The infusion time may be longer at the Investigator's discretion based on local infusion site-related symptoms up to a maximum of 4 hours. VIS410 or placebo will be administered within 48 hours of being prepared by the study pharmacist.

Pretreatment: Subjects will be given a pretreatment regimen of diphenhydramine 50 mg PO and ibuprofen 400 mg PO or acetylsalicylic acid 325 mg PO 60 minutes before IV infusion. If the subject has any history of delayed gastric emptying, including premenstruation syndrome or menstruation, the subject may receive premedications 120 minutes prior to IV infusion.

Following administration, subjects will be observed for at least 2 hours at the infusion center and discharged if considered safe by the investigator. Prior to discharge, all subjects will be counseled on the potential GI AEs and management of these events.

Study Duration:

The total study duration for each subject (screening through study exit) will be approximately 14 weeks (Day 100).

Criteria for Evaluation:

Primary Endpoints:

- The proportion of subjects with adverse events (AEs) and serious adverse events (SAEs) following administration of VIS410
- The proportion of subjects with treatment-emergent AEs (TEAEs) including hypersensitivity reaction, anaphylactic reaction, and AEs of special interest (AESIs) following dosing

Secondary Endpoints:

- The incidence, severity, and duration of signs and symptoms of influenza-like illness as assessed by the Influenza Patient Reported Outcomes questionnaire after a single IV dose of VIS410
- Percentage of participants requiring hospitalization for influenza-related complications
- Duration of hospitalization for influenza-related complications
- Percentage of participants with complications of influenza
- Percentage of participants with influenza A relapse/reinfection
- VIS410 pharmacokinetic (PK) parameters (C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-last}, $t_{1/2}$, V_d, CL) in serum
- The difference between VIS410 and placebo treatment groups in viral AUC from nasopharyngeal swabs
- The difference between VIS410 and placebo treatment groups in peak viral load and time to resolution of viral load from nasopharyngeal swabs
- Titer of anti-VIS410 antibody-positive samples

Exploratory Endpoints:

- PK parameters (C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-last}, $t_{1/2}$) of VIS410 from nasopharyngeal secretions

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- Genotypic and phenotypic assessment to determine the emergence of VIS410-resistant viruses
- Correlations between serum and/or nasopharyngeal PK with viral load, clinical symptoms, presence of anti-drug antibodies, and additional endpoints
- Titer of anti-influenza A antibodies by hemagglutinin inhibition assay (HAI) in serum
- Correlations between virology and safety parameters and/or additional parameters may be explored

Statistical Methods:

Sample size:

Approximately one hundred fifty (150) subjects. No formal sample size calculations were done for this study. The sample size is consistent with Phase 2a studies to assess safety and tolerability. VIS410 endpoints will compare aggregated VIS410 data as well as different dose levels of VIS410 to the placebo arm.

Descriptive analyses of data from subjects will be performed for demographic characteristics, AEs, concomitant medication use, and PK parameters in serum and nasopharyngeal secretions as described below. All calculations will use the actual times recorded in the electronic data capture (EDC) system for dosing and sampling. Individual and mean (± standard deviation [SD]) or median concentrations versus time profiles will be plotted by study period on both linear and logarithmic scales. Additional plots and PK parameters may be generated as appropriate.

Serum Pharmacokinetics

Serum concentrations and the computed PK parameters will be listed by subject for VIS410. Summary statistics of serum concentrations and PK parameters will be presented including means, geometric means, standard deviations, CV, medians and ranges, as appropriate. Additional analyses and summaries may be generated as appropriate.

The following PK parameters will be determined for VIS410 in serum:

- C_{max}: maximum observed serum concentration
- T_{max}: time of C_{max}
- $AUC_{0-\infty}$: area under the serum concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-last}: area under the serum concentration-time curve from time 0 to the last measurable concentration
- $t_{1/2}$: terminal elimination half-life
- CL: total clearance
- V_d: volume of distribution

PK data from this study will be also analyzed by population PK modeling.

Nasopharyngeal Secretion Pharmacokinetics

Nasopharyngeal secretion concentrations and the computed PK parameters will be listed by subject for VIS410. Summary statistics of nasopharyngeal secretion concentrations and PK parameters will be presented including means, geometric means, standard deviations, CV, medians and ranges, as appropriate. Additional analyses and summaries may be generated as appropriate.

The following PK parameters will be determined for VIS410 from nasopharyngeal secretions:

- C_{max}: maximum observed concentration from nasopharyngeal secretions
- T_{max}: time of C_{max}
- $AUC_{0-\infty}$: area under the nasopharyngeal secretion concentration-time curve from time 0 extrapolated to infinity

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- $AUC_{0\text{-last}}$: area under the nasopharyngeal secretion concentration-time curve from time 0 to the last measurable concentration
- $t_{1/2}$: terminal elimination half-life
- Ratio of nasal:serum AUC

Additional PK parameters may be determined as appropriate.

Adverse Events

The original terms in the EDC system used by Investigators to identify AEs other than symptoms of influenza A will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA current version 19). The reported AEs will be allocated to phases based on their start date. All AEs will be listed. All AEs with onset during the treatment phase (i.e., TEAEs) will be summarized.

AEs will be summarized by treatment group and by MedDRA body organ system and preferred term, severity, relatedness, and seriousness.

The difference in proportions of subjects with AEs, TEAEs, AESIs, and SAEs between treatment groups and their 95% CI will be calculated (primary safety endpoint).

Special attention will be paid to those subjects who died, discontinued the study drug due to an AE, or experienced a severe or serious AE. Summaries, listings, and narratives may be provided, as appropriate.

Injection Site Tolerability

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

Complications of Influenza

Complications of influenza are defined as pneumonia, myocarditis, worsening of chronic bronchitis, other chronic pulmonary diseases, sinus infection, otitis, and death. Complications of influenza will be reported by variable, treatment group, and time point.

Clinical Laboratory Tests

Actual values and changes from baseline of each continuous biochemistry, hematology and urinalysis test will be evaluated by means of descriptive statistics by assessment time point and by treatment group. For categorical urinalysis tests, frequency tables of actual values will be provided by assessment time point and by treatment group.

Relative changes in clinical laboratory test values compared to values at baseline will be evaluated according to the DMID grading table or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined. A shift from baseline table of the abnormalities will be provided by assessment time point and by treatment group.

A listing of subjects with any clinical laboratory test result outside the reference ranges will be provided.

Vital Signs

Actual values and changes from baseline of heart rate, respiratory rate, temperature, systolic blood pressure (SBP), and diastolic blood pressure (DBP) measurements will be evaluated by means of descriptive statistics by assessment time point and by treatment group.

A shift from baseline table of vital sign abnormalities will be provided by assessment time point and by treatment group.

Electrocardiography

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, and QT interval. Values for QT corrected for heart rate (QTc) will be derived. QTc corrected according to Fridericia (QTcF) [6] will be the

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primary correction parameter.

Actual values and changes from baseline of ECG variables will be evaluated by means of descriptive statistics by assessment time point and by treatment group.

A shift from baseline table of ECG abnormalities will be provided by assessment time point and by treatment group. For absolute QTcF interval prolongation (>450, >480, >500 msec) and changes from baseline (increase >30 and >60 msec), a frequency table by assessment time point and by treatment group will be provided.

Signs and Symptoms of Influenza

- Frequency tabulation of the occurrence and severity of each of the subject-reported symptoms of influenza-like illness by assessment time point and by treatment group
- Descriptive statistics of the duration of each of the subject-reported symptoms of influenza-like illness by treatment group

Immunology

Immunological assessments will be summarized by parameter, treatment group, and time point using descriptive statistics:

- Anti-VIS410 antibody titers by ADA in serum
- Anti-influenza A antibodies by HAI in serum
- HAI levels to determine a proper immune response to the influenza infection

Exploratory Pharmacokinetic/Pharmacodynamic Analyses

Various techniques will be used to explore exposure–response relationships, and to compare the strength of the relationship between each independent variable (e.g., AUC, C_{max}, and concentration at specific time point) and the dependent variables (e.g., viral AUC, peak viral load, and time to cessation of viral shedding, clinical symptoms, and additional endpoints). These techniques may include graphical and statistical methods, including the creation of boxplots, spaghetti plots, histograms, and a variety of linear, nonlinear, or logistic regression techniques and time-to-event methods. If appropriate, continuous independent variables will be evaluated as such, and as categorical variables (grouping subjects into exposure categories).

Anti-Drug Antibodies

Anti-VIS410 antibody titer will be summarized by treatment group and time point using descriptive statistics.

Physical Examination

Abnormal findings in physical examination will be listed.

TIME AND EVENTS SCHEDULE

Table 1. Schedule of Assessments

Study Time Point	Screening [1]	Day 1					Clinic Visit Day						
		Baseline [1]	Predose	0 hour	End of Infusion	≥2 Hours from End of Infusion	3 (±1) [2]	5 (±1) [2]	7 (±1)	14 (±3)	28 (±3)	56 (±7)	100 (±7) FU/ET [3]
Screening/Administrative Assessments													
Informed consent	X												
Inclusion/exclusion criteria	X												
Medical history and demographics	X												
Admission		X											
Discharge						X							
Nasopharyngeal swab for Rapid flu test [4]	X												
Onset of symptoms interview	X												
Randomization		X											
Safety Assessments [5]													
Supine ECG [6]	X				X								
Vital signs [7]	X	X [8]			X	X	X	X		X	X	X	X
Body temperature [9]	X	X [8]			X	X	X———			———X	X	X	X
Physical exam	X												
Targeted physical exam [10]		X [8]				X	X	X	X	X	X	X	X
Urine pregnancy test [11]	X												X
Serology (HIV rapid test) [12]	X												
Chemistry [13]	X							X		X			X

Study Time Point	Screening [1]	Day 1					Clinic Visit Day						
		Baseline [1]	Predose	0 hour	End of Infusion	≥2 Hours from End of Infusion	3 (±1) [2]	5 (±1) [2]	7 (±1)	14 (±3)	28 (±3)	56 (±7)	100 (±7) FU/ET [3]
Hematology [13]	X							X		X			X
Urinalysis [13]	X							X		X			X
Instructions conmeds and FluPRO	X												
Observation in unit				X	X	X							
FluPRO completion [14]		X					X——	——	——	——X			
FluPRO compliance						X	X	X	X				
FluPRO collection, review and reinstructions							X	X	X				
AESIs		X——	——	——	——	——	——	——	——	——	——X		X [15]
Concomitant therapy, AEs [2]		X——	——	——	——	——	——	——	——	——	——	——	——X
Collection of SAEs		X——	——	——	——	——	——	——	——	——	——	——	——X
Influenza complications		X——	——	——	——	——	——	——	——	——	——	——	——X
Study Agent Administration/Virologic/PK, and Immunogenicity Assessments													
Pretreatment medications – 1 hour (±5 min) prior to start of infusion [16]			X										
VIS410/placebo infusion [17]				X									
Serum PK			X [18]		X [19]		X	X	X	X	X	X	X
Nasopharyngeal swab [20]			X [18]				X	X	X	X [21,22]	X [21,22]	X [21,22]	X [21,22]
Serum ADA			X							X		X	X
Serum HAI sample			X							X	X		

[1] Screening and baseline activities may be performed on the same day.

[2] Subjects will have a follow-up phone call in the evening of the dosing day to ensure subjects' safety and well-being. In addition, between clinic visits up to Day 7 (e.g., Days 2, 4 and 6), subjects will receive a follow-up telephone call to ensure compliance with FluPRO Influenza Symptom Questionnaire and review any new or worsening signs or symptoms.

[3] Subjects who terminate the study early will return to the clinical site within 14 days after discontinuation for safety assessments. See Section 8.2 for discharge procedure in case of early termination. All other subjects will return for a final follow-up visit at Day 100 ±7 days.

[4] Single nasopharyngeal swab will be obtained from one nostril.

[5] Safety Assessments may be performed at another time, if considered needed at the Investigator's discretion. In case unexpected symptoms are noticed in subjects, additional safety assessments might be performed.

[6] Single 12-lead ECG will be performed after a 5-min rest in supine position. Any significant elevation of QTc>500 msec/min should trigger repeat confirmation in triplicate.

[7] Vital signs should be measured after 5 minutes of rest in a supine position and include heart rate, respiratory rate and blood pressure. Vital signs will only be measured while the subject is in the clinic.

[8] Only if screening and baseline are not on the same day.

[9] Body temperature will be measured twice daily from Days 1 through 10 (inclusive) and then once at each follow-up visit. Self-measurement will be done by the subject when not in the clinic preferably at approximately the same times each day.

[10] A targeted physical exam may be performed at the Investigator's or his/her designee's discretion.

[11] A pregnancy test will be performed for all female subjects of childbearing potential.

[12] For patients with no documented HIV status within 3 months prior to the screening visit, a rapid HIV test will be conducted. Consent for this testing will be obtained prior to conducting any HIV testing. All positive rapid tests will be followed up according to local requirements. Patients with documented HIV positive status are assessed according to Exclusion 12 for eligibility.

[13] See Laboratory Assessments for list of tests in Appendix 1.

[14] FluPRO questionnaire will be completed at home between clinic visits through Day 10 (inclusive).

[15] Only for subjects who terminate early within 28 days after study drug infusion.

[16] If the subject has any history of delayed gastric emptying, including premenstruation syndrome or menstruation, the subject may receive premedications 120 minutes prior to IV infusion.

[17] Subjects will be observed during infusion and at least 2 hours after completing the infusion of VIS410 to allow monitoring for possible hypersensitivity reactions. VIS410 will be administered over 2 hours. Infusion time can be extended at discretion of the Investigator up to 4 hours based on local infusion-related symptoms. If any serious systemic reactions occur, the infusion of VIS410 can be slowed or stopped at the discretion of the Investigator.

[18] Within 1 hour prior to VIS410 administration.

[19] Sample collected within 30 minutes after completing the infusion of VIS410/placebo.
[20] Nasopharyngeal swabs will be obtained from both nostrils (1 swab per nostril).
[21] Will be done for the first 50 subjects enrolled only.
[22] If a subject presents with or reports influenza-like illness, additional swabs (1 swab per nostril) should be taken (see Section 7.1.5).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity
AUC_{0-last}	Area under the concentration-time curve from time 0 to the last measurable concentration
CD-1	Cluster of differentiation 1
CL	Clearance
C_{max}	Maximum serum concentration
CRO	Contract Research Organization
DBA	Dilute Brown Non-Agouti
DBP	Diastolic blood pressure
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
EC_{50}	Half-maximal effective concentration
EDC	Electronic data capture system
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HA	Hemagglutinin
HAI	Hemagglutination inhibition assay
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NOAEL	No-observed-adverse-effect level
NSAID	Non-steroidal anti-inflammatory drug
PK	Pharmacokinetic
PO	Oral (by mouth)
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Elimination half-life
$TCID_{50}$	Half-maximal tissue culture infective dose

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
t_{max}	Time corresponding to maximum serum concentration
V_d	Volume of distribution

Definitions of Terms

BMI	Body Mass Index, Weight in kilogram divided by the square of height in meters
Study drug	VIS410 or placebo
VIS410	Investigational product

1. INTRODUCTION

1.1 BACKGROUND INFORMATION

Severe influenza disease is a common occurrence each season, especially in high-risk groups such as young children, older adults, patients with pulmonary conditions, inflammatory conditions, malignancies, and pregnant women [1,2]. Despite available therapy with neuraminidase inhibitors, including oseltamivir (Tamiflu®; Roche; oral), zanamivir (Relenza®; GlaxoSmithKline; inhaled), and peramivir (Rapivab™; Biocryst; IV), 10%-44% of hospitalized patients require intensive care and 25%-50% of these patients die. In the United States, it is estimated that more than 200,000 patients are hospitalized with influenza each year, with up to 48,000 deaths per year [3].

The therapeutic use of passive polyclonal antibodies to prevent viral infections, including hepatitis B, varicella, cytomegalovirus, rabies, and respiratory syncytial virus has been well established. More recently, monoclonal antibodies for viral infections have been developed, including palivizumab (Synagis®), a Food and Drug Administration-licensed treatment for the prevention of respiratory syncytial virus infection.

Visterra has developed a novel approach to antibody discovery whereby functionally conserved epitopes are identified based on atomic interaction networks and targeted with rationally engineered human antibodies. Using this approach, VIS410, a broad spectrum human immunoglobulin G1 (IgG1) monoclonal antibody with demonstrated efficacy against both Group 1 (including H1 and H5) and Group 2 (including H3 and H7) influenza strains, in both treatment and prevention models of influenza, was developed. Visterra intends to develop this product for treatment of influenza A, specifically in severely ill hospitalized patients.

This study will provide the first indications of safety and tolerability of VIS410 in subjects infected with uncomplicated seasonal influenza A. Efficacy as measured by signs and symptoms will also be collected although the sample size does not support statistically significant determination of efficacy.

1.2 NONCLINICAL STUDIES

Pharmacology, Pharmacokinetics, and Metabolism

VIS410 is a human IgG1 monoclonal antibody with a high sequence homology to human germ line sequences. VIS410 broadly neutralizes influenza A strains in vitro, with half-maximal inhibitory concentration values of approximately 0.1-11 μg/mL. Mechanistic studies indicate that VIS410 inhibits hemagglutinin (HA)-mediated cell membrane fusion, thus preventing viral replication.

In vivo studies have demonstrated that VIS410 administered to mice in prevention and treatment models of influenza, at doses between 1 and 20 mg/kg (either 24 hours pre-exposure or 24-72 hours post-exposure) can protect mice challenged with influenza A strains (influenza A/Puerto Rico/8/1934 [H1N1], influenza A/Victoria/3/1975 [H3N2], and influenza A/Vietnam/1203/2004 [H5N1]). Additionally, in vivo studies in ferrets have demonstrated that treatment with VIS410 can reduce the transmission of influenza pH1N1 via

respiratory droplets. The serum concentrations of VIS410 associated with prevention of infection in ferrets should be readily achievable in humans also. VIS410 also demonstrates protection against a newly emerging highly pathogenic H7N9 (A/Anhui/1/2013) strain of influenza in a severe Dilute Brown Non-Agouti (DBA) mouse model [4].

Toxicology

In a cynomolgus monkey Good Laboratory Practice (GLP) toxicity/toxicokinetics study, 4 IV doses of VIS410 were administered over a 28-day period at 5, 50, and 250 mg/kg with no clinically significant findings. Based on this GLP study, the no-observed-adverse-effect level (NOAEL) was considered to be 250 mg/kg and the half-life ($t_{1/2}$) of VIS410 was determined to be 8–9 days.

In the cynomolgus monkey toxicology study, VIS410 was administered as an IV infusion over 10 minutes and no infusion reactions were observed.

In a mouse GLP toxicity/toxicokinetics study (VIS410 IV 4 doses at 5, 50 and 250 mg/kg, infused over 14 days to 384 mice), 14 mice (3.6%) died 1-2 hours after Day 14 dosing in the 5 and 50 mg/kg dose groups. This was likely due to an expected immunogenic response in mice, as VIS410 is a human antibody, and not a toxic response. The NOAEL was considered to be 250 mg/kg.

In vitro tissue cross-reactivity studies of VIS410 with normal human tissues, cynomolgus monkey tissues, and cluster of differentiation 1 (CD-1) mouse tissues showed VIS410 to be broadly cross-reactive. VIS410 staining of membrane was limited to cells within the surface/mucosal epithelium in colon, small intestine, and fallopian tube. Of note, staining was not observed in vivo, in tissues from toxicology studies in monkeys or mice when assessed by immunohistochemistry post-sacrifice.

The lack of toxicity in the in vivo cynomolgus monkey and mouse toxicology studies suggests that the cross-reactivity findings were of little toxicological significance.

An in vitro soluble cytokine release assay performed using human whole blood at VIS410 concentrations that encompass the expected concentrations of VIS410 in human blood when administered as IV doses of 2 to 50 mg/kg, did not stimulate any acute or sustained release of any pro-inflammatory cytokines.

1.3 CLINICAL STUDIES

Phase 1 (VIS-C001). In a Phase 1 study (VIS-C001), a total of 30 healthy volunteers received a single, 120-minute IV infusion of 2, 5, 15, 30, or 50 mg/kg of VIS410 (200 mL volume) (6 subjects per cohort) and 11 subjects received a single, 120-minute IV infusion of placebo (sodium chloride 0.9%; 200 mL volume).

The PK and safety data are presented below.

Pharmacokinetics

PK profiles of the serum and nasopharyngeal samples demonstrated that VIS410 exposure was approximately proportional to the dose administered with a mean serum $t_{1/2}$ of 12.9 days. This $t_{1/2}$ is within the expected range for the IgG1 molecules. In addition, the 13-day $t_{1/2}$

supports the single dosing of VIS410, as the circulating levels should be sufficiently high during the normal course of an influenza infection in hospitalized patients (5–14 days). The maximum concentration (C_{max}) values in the serum for the 30 and 50 mg/kg cohorts were 980 and 1316 µg/mL, respectively.

Nasopharyngeal swabs were taken from the 15, 30, and 50 mg/kg cohorts for upper respiratory pharmacokinetics. The nasopharyngeal PK profiles were approximately dose proportional. Mean nasal C_{max} values at the 30 and 50 mg/kg dose levels were 20.0 and 25.3 µg/mL, respectively.

Safety

Overall, VIS410 was generally safe and well tolerated at all dose levels studied. Treatment-emergent adverse events (TEAEs) were reported for 20/30 (66.7%) subjects receiving VIS410 and 7/11 (63.6%) subjects receiving placebo. There were no drug-related serious adverse events (SAEs), no drug-related discontinuations, and no infusion-related reactions such as anaphylaxis or injection site reactions.

Notable adverse events (AEs) included one unrelated SAE of leukopenia and esophagitis secondary to primary HSV-1 infection in one subject (VIS410, 30 mg/kg cohort). This SAE resolved and the subject is doing well. Another unrelated SAE of acute appendicitis was also reported (placebo cohort).

The most common AEs observed were diarrhea (10/41, 24.4%) and headache (8/41, 19.5%). All diarrheal or loose stool AEs were observed in the VIS410-treated subjects and were usually mild to moderate, started ~2–4 hours after dosing, were transient and resolved spontaneously within 24 hours after dosing with no associated dehydration. The gastrointestinal (GI) events were dose proportional and the majority of the AEs were observed at the highest dose tested (50 mg/kg). None of the GI events were associated with a systemic allergic reaction or elevation in liver or biliary laboratory values. Mean hematology, serum chemistry, and urinalysis results were within the normal limits and the mean values and changes from baseline were similar across the treatment groups and placebo. Overall, mean vital sign measurements observed after dosing were similar to those observed at baseline. Mean changes from baseline were also similar across VIS410 dose levels, and no apparent treatment- or dose-related trends were observed.

The anti-drug antibody (ADA) data demonstrated a low level of positive ADA in 4 out of 30 subjects receiving VIS410 (Table 2). The subjects with positive ADA did not demonstrate any impact on their PK profile.

Table 2. Study VIS-C001 ADA Data

Cohort Dose (mg/kg)	No. of Confirmed ADA Positive	Pre-Infusion Titer	Confirmed Day	Positive Titer
2	0/6	None detected	NA	None detected
5	3/6	None detected	120	titer 10
		None detected	14	titer 10
			120	titer 40
		None detected	120	titer 40
15	1/6	None detected	120	titer 40
30	0/6	None detected	NA	None detected
50	0/6	None detected	NA	None detected

Phase 2a Challenge Study (VIS410-201). Study VIS410-201, "A Phase 2a Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability and Antiviral Activity of a Single Intravenous Dose of VIS410 in Healthy Subjects after a Viral Inoculation with Influenza A (H1N1)," was conducted at a single site in Antwerpen, Belgium by SGS Life Sciences. Briefly, 24 hours after inoculation with a 10^6 tissue culture infective dose (TCID) of naturally attenuated influenza A (H1N1) virus [7], subjects receive a single IV administration of VIS410 (2300 mg fixed dose, equivalent of 30 mg/kg) or placebo (7:5 randomization to VIS410:placebo). Subjects were quarantined 10 days post-inoculation and discharged thereafter.

A total of 46 subjects were treated with VIS410 (n=33) or placebo (n=13) across 5 cohorts. Cohorts were performed sequentially and included different pretreatment regimens used to mitigate the GI events observed with VIS410. Preliminary findings from the first 31 subjects are presented below.

Preliminary Efficacy Data

A partially blinded pre-specified interim analysis of the first 3 cohorts was conducted to evaluate the safety and efficacy of the 2300 mg VIS410 dose and to determine whether dose escalation was appropriate. The distribution of subjects is presented in Table 3.

Table 3. Distribution of Subjects

Treatment	No. Dosed	Per Protocol*	No. Infected**
Placebo	13	9	7
VIS410 (2300 mg)	18	16	13
Total	31	25	20

HAI = hemagglutinin inhibition assay positive seroconversion at Day 14 or 28.
*Subjects with HAI >10 at baseline excluded per inclusion/exclusion criteria.
**Infected subjects who are either polymerase chain reaction positive or HAI positive.

Based on the preliminary results, VIS410 2300 mg dose demonstrated a statistically significant antiviral effect with a 76% and 91% reduction in nasopharyngeal viral AUC by

quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and half-maximal tissue culture infective dose ($TCID_{50}$) compared to placebo (Table 4).

Table 4. Viral Load and AUC Data

Viral Measure	Placebo (N=7)	VIS410 (N=13)	Reduction (%)	p Value*
Median Viral AUC $TCID_{50}$ (log_{10} X hours)	546	45	92	0.019
Median Viral AUC qPCR (log_{10} X hours)	1031	235	77	0.024
Median Peak Viral Load $TCID_{50}$ (log_{10})	5.0	2.7	2.2	0.009
Median Peak Viral Load qPCR (log_{10})	7.1	5.6	1.5	0.043

*Calculated with Mann-Whitney U Test.

In addition, analysis of the symptoms data demonstrated a trend in respiratory symptom resolution that was consistent with the virology data. Although this study was not powered to detect a statistical difference in symptom relief, a 2-day reduction in resolution of upper respiratory symptoms and AUC was observed in the VIS410 2300 mg group vs. placebo.

Preliminary Safety Data

In the first cohort, 7 subjects received 2300 mg of VIS410 while 5 subjects received placebo. Moderate to severe cramping, loose stool and/or diarrhea were reported in 6 of the 7 subjects receiving VIS410 and none of the placebo subjects. Most symptoms were observed either during the infusion or within 30 minutes of the end of infusion and resolved within ~12 hours. Given the association with infusion, these AEs were all considered possibly related to the study drug. In subsequent cohorts, the addition of a pretreatment regiment containing diphenhydramine mitigated the GI AEs and VIS410 was generally well tolerated with a reduction in frequency and the severity of GI events from moderate/severe to mild.

As statistically significant efficacy was demonstrated with the 2300 mg dose in the first 3 cohorts, the protocol was amended to optimize the tolerability of VIS410. This was done by testing different pretreatment regimens and escalating the dose of VIS410 to 4600 mg in the context of the virus challenge model. This portion of the study (designated as Part 2) was open label; however, virological data were collected to understand viral response and pharmacokinetics/pharmacodynamics.

Eleven subjects were enrolled in Cohort 4 and were inoculated with H1N1 influenza virus and administered VIS410 2300 mg 24 hours later. Four subjects were pretreated with diphenhydramine 50 mg PO and montelukast 10 mg PO (Group1); 4 subjects were pretreated with diphenhydramine 50 mg PO and ibuprofen 600 mg PO (Group 2); and 3 subjects were pretreated with diphenhydramine 50 mg IV and montelukast 10 mg PO (Group 3).

Three subjects in Groups 1 and 3 subjects in Group 3 experienced transient loose stool that resolved spontaneously. Only 1 of 4 subjects in Group 2 pretreated with diphenhydramine and ibuprofen experienced mild and transient loose stools. Based on these results it was determined that the regimen of diphenhydramine plus ibuprofen resulted in the best tolerability profile and this pretreatment regimen was further assessed in 4 subjects at the

4600 mg dose of VIS410 following viral challenge. Overall, 4600 mg VIS410 following pretreatment was generally well tolerated. None of the 4 subjects reported cramping or any other symptoms associated with severe infusion reactions. Mild and transient loose stools were observed in 3 of the subjects. A fourth subject had a transient episode of nausea and vomiting about 8.3 hours after the start of infusion. All events were considered resolved within 24 hours of onset.

Phase 1 (VIS410-102) Study VIS410-102 is a Phase 1, randomized, placebo-controlled study to evaluated safety, tolerability, and PK of a single 2300 mg and 3800 mg dose of VIS410 following administration of different pretreatment regimens. A total of 83 subjects received study drug (Placebo (n=12), VIS410 2300 mg (n=59), VIS410 3800 mg (n=12)). VIS410 2300 mg was evaluated at a 2-hour infusion (n=12), 4-hour infusion (n=12), 2-hour infusion following a pretreatment regimen of diphenhydramine 50 mg PO and ibuprofen 400 mg PO 60 minutes before infusion (n=12), 2-hour infusion following a pretreatment regimen of cetirizine 10 mg PO 60 minutes before infusion (n=12), and 2-hour infusion following a pretreatment regimen of diphenhydramine 50 mg PO and acetylsalicylic acid 325 mg PO 60 minutes before a 2-hour infusion (n=11). The 3800 mg VIS410 dose was evaluated at a 2-hour infusion following a pretreatment regimen of diphenhydramine 50 mg PO and ibuprofen 400 mg PO 60 minutes before infusion (n=12). The pretreatment regimens were selected in order to mitigate the GI AEs observed with VIS410. This study is currently ongoing and a preliminary summary of safety data to date is presented below.

To date there have been no reports of SAEs. One subject at the 3800 mg dose discontinued study drug infusion due to AEs of nausea, vomiting, chills, and hot flashes. All events resolved after study drug discontinuation despite slow decrease in serum concentration of VIS410. VIS410 was not associated with any signs or symptoms that are consistent with systemic allergic reactions or anaphylaxis. Gastrointestinal events were observed at a higher frequency in the VIS410 treated subjects compared to Placebo. Based on the data from the 2300 mg and 3800 mg dose groups, VIS410 was associated with GI events ranging from mild to severe; however, a 2300 mg dose of VIS410 with a single-dose pretreatment regimen of diphenhydramine and low dose ibuprofen or acetylsalicylic acid was associated with a low rate of GI events (16.7% and 9.1%, respectively). Overall, the most commonly reported events were loose stool, diarrhea, and abdominal cramping. Subjects who received no pretreatment regimen had the highest number of GI AEs ranging from mild to severe. The prolonged infusion of VIS410 (over 4 hours) resulted in a larger number of GI events than the 2-hour infusion (41 events in 10 subjects vs. 18 events in 6 subjects, respectively), suggesting that GI events will not be mitigated by slowing the infusion rate. Pretreatment regimens of an antihistamine (cetirizine) or an antihistamine (diphenhydramine) plus a prostaglandin inhibitor (ibuprofen or acetylsalicylic acid) mitigated the GI events compared with the no pretreatment cohorts. The rate (13 GI events in 7 subjects) and severity of events (12/13 mild) were slightly lower in the cetirizine group than the no pretreatment groups. The lowest rate of GI events with VIS410 was observed in subjects who received the diphenhydramine plus acetylsalicylic acid pretreatment regimen, with only 1 subject reporting a mild episode of loose stool and abdominal pain approximately 22 hours after initiation of study drug administration that resolved spontaneously with no intervention. Another effective pretreatment regimen included diphenhydramine plus ibuprofen at both 2300 and 3800 mg

dose, with only 2 subjects in the 2300 mg dose group reporting a mild episode of loose stool 7 to 9 hours after initiation of study drug administration that resolved spontaneously with no intervention and 1 report of mild nausea in the same subject. The same pretreatment with a higher dose of 3800 mg, showed a low rate of GI events with 1 subject reporting a mild episode of loose stool approximately 21 hours after start of infusion and another subject reporting mild nausea. Both events resolved spontaneously with no intervention. In addition, one (1) subject at the 3800 mg dose discontinued study drug infusion due to AEs of nausea, vomiting, chills, and hot flashes.

To date, no clinically significant changes have been observed in hematology, chemistry, and urinalysis parameters. Specifically, no alterations in electrolytes were observed in the subjects with loose stool or diarrhea.

In summary, the type and timing of GI AEs observed in this study are consistent with prior studies, are mostly mild in intensity, are self-limiting in nature, and resolve following the completion of infusion with no sequelae. These data suggest that a pretreatment regimen is necessary to mitigate the GI events associated with VIS410; however, an antihistamine alone may not be as effective in mitigating the AEs. Addition of a prostaglandin inhibitor/non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or acetylsalicylic acid to an antihistamine was necessary to further reduce the frequency and severity of GI events. These data were consistent with previous safety data in an influenza virus challenge study where a regimen of diphenhydramine and ibuprofen mitigated the severity and or frequency of GI AEs in 8 subjects given 2300 mg (n=4) and 4600 mg of VIS410 (n=4).

For more detailed information on VIS410, refer to the current Investigator Brochure [5].

1.4 OVERALL RATIONALE FOR THE STUDY

This study will be used to determine the safety and efficacy of VIS410 in subjects with seasonal influenza A and is an important study for progression of the program toward testing in hospitalized subjects with severe influenza.

1.5 RISK BENEFIT ANALYSIS

In animal studies, single or multiple dose administrations of VIS410 were generally well tolerated at doses of up to 250 mg/kg. In the Phase 1 VIS-C001 study in 41 subjects (see Section 1.3), all doses studied were generally safe and well tolerated with only mild to moderate loose stool or diarrhea seen at the highest doses administered (30 and 50 mg/kg). The most common AE was a mild/Grade 1 loose stool or diarrhea that was self-limiting. In the Phase 2a challenge study (VIS410-201), administration of 2300 mg of VIS410 in the context of an influenza infection resulted in 6 of 7 subjects having moderate to severe cramping and loose stools that mostly resolved within 10 hours. Following this initial cohort study, a pretreatment regimen was implemented using antihistamines including diphenhydramine that resulted in 4 of 5 pretreated subjects in the VIS410 arm experiencing mild stomach discomfort. An additional open-label tolerability study tested several pretreatment regimens including diphenhydramine and ibuprofen in the influenza-infected volunteers. Following dosing of 2300 mg of VIS410 in the ibuprofen and diphenhydramine

pretreatment group, the subjects tolerated VIS410 well with only 1 of 4 subjects experiencing any GI AE and this was a mild transient loose stool without any associated cramping. At 4600 mg of VIS410, pretreatment with ibuprofen and diphenhydramine was also generally well tolerated with no associated cramping. Transient and mild loose stools were reported in 2 of the 4 subjects and 1 subject also had a transient episode of nausea and vomiting. The AEs observed to date with the projected therapeutic dose of 2300 mg were mostly GI events, were mild to moderate in intensity, resolved spontaneously with no additional intervention, and decreased in severity and frequency following pretreatment with ibuprofen and diphenhydramine. Considering the potential benefit of VIS410 in treatment of severe influenza A infection and the types and severity of AEs observed to date at the 2300 mg dose, the benefit outweighs the risk of further evaluation of VIS410 in patients with influenza A infection.

1.5.1 *Potential Risks*

As described above, some subjects may experience cramping and/or a transient loose stool or diarrhea. Animals that received VIS410 as either treatment or prophylaxis experienced decreased weight loss compared with vehicle/placebo-treated animals following challenge with various strains of influenza virus. In mice treated with 4 doses of VIS410 over 14 days, 14 of 384 animals had severe systemic hypersensitivity (anaphylaxis) with death within 1-2 hours after the fourth dose; and ADAs were found in 8 animals at the end of the 28-day recovery period. This was not considered to be a VIS410 specific effect as the NOAEL was 250 mg/kg but rather a consequence of immunological response in mice to a human antibody. Other human antibodies have elicited ADA in mice without clinical problems in humans.

Administration of VIS410, IV once weekly for 4 weeks in a non-human primate model of cynomolgus monkeys was well tolerated. All animals survived and there were no abnormal clinical observations suggesting distress to the animals (hypersensitivity-related or other) throughout the duration of the study period (including the administration or recovery periods).

ADAs were elicited in 3 of the 42 (7%) samples that had a reduction in titers that were most likely due to drug exposure. As with the mice, there were no findings suggesting VIS410 toxicity in clinical, laboratory or pathology examinations.

In an in vitro soluble cytokine release assay performed using human whole blood, VIS410 did not stimulate any dramatic or pervasive release of any pro-inflammatory cytokine (see Section 1.2).

Pharmacological class effects commonly associated with marketed monoclonal antibody products used for treatment in humans include serious infusion reactions including anaphylaxis (see Section 1.3). VIS410 is to be administered as a single infusion and is directed at an exogenous viral target. As a result, it is considered to be of low probability that other SAEs such as infection risks reported for approved monoclonal antibodies directed against endogenous human protein targets such as immune modulating cytokines and often administered as multiple doses over a long period will be observed with VIS410.

As described in Section 1.3, a single administration of VIS410 to healthy volunteers was safe and well tolerated. The potential exists for subjects to experience cramping or loose stools, but pretreatment with histamine antagonists (diphenhydramine) with an NSAID such as ibuprofen or acetylsalicylic acid ameliorated the GI effects.

Given the potential for acute severe hypersensitivity and other adverse reactions observed with other monoclonal antibody therapies, subjects should be closely monitored for relevant signs and symptoms following administration of VIS410. VIS410 should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

1.5.2 *Potential Benefits*

Animals that received VIS410 as either treatment or prophylaxis experienced prolonged survival compared with vehicle/placebo-treated animals following challenge with various strains of influenza A virus. The Phase 2a challenge study demonstrated a statistically significant reduction in viral AUC following treatment with VIS410 compared with placebo (Section 1.3).

At this time, the actual benefits of VIS410 for the treatment of influenza patients are unknown. However, data from a recently conducted human challenge study in 31 healthy volunteers given influenza A demonstrated a statistically significant decrease in shedding of influenza virus with a shorter duration of symptoms (2 days) in the VIS410-treated group compared with the placebo group.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- Assess the safety and tolerability of a single intravenous (IV) dose of VIS410 in patients with uncomplicated influenza infection

2.2 SECONDARY OBJECTIVES

- Evaluate the efficacy of VIS410 compared with placebo on the time to alleviation of clinical symptoms of acute uncomplicated influenza
- Evaluate the effect of VIS410 on severity of influenza infection
- Assess the pharmacokinetics of VIS410 in serum
- Assess the effects of VIS410 on viral shedding
- Assess the immunogenicity of VIS410

2.3 EXPLORATORY OBJECTIVES

- Assess the pharmacokinetics of VIS410 from nasopharyngeal secretions
- Assess viral isolates to determine the emergence of VIS410-resistant viruses
- Assess correlations between virology, safety, pharmacokinetics, viral shedding, clinical symptoms, and other endpoints
- Assess the anti-influenza immune response

3. STUDY ENDPOINTS

3.1 PRIMARY ENDPOINTS

- The proportion of subjects with adverse events (AEs) and serious adverse events (SAEs) following administration of VIS410
- The proportion of subjects with treatment-emergent AEs (TEAEs) including hypersensitivity reaction, anaphylactic reaction, and AEs of special interest (AESIs) following dosing

3.2 SECONDARY ENDPOINTS

- The incidence, severity, and duration of signs and symptoms of influenza-like illness as assessed by the Influenza Patient Reported Outcomes questionnaire after a single IV dose of VIS410
- Percentage of participants requiring hospitalization for influenza-related complications
- Duration of hospitalization for influenza-related complications
- Percentage of participants with complications of influenza
- Percentage of participants with influenza A relapse/reinfection
- VIS410 PK parameters (C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-last}, $t_{1/2}$, V_d, CL) in serum
- The difference between VIS410 and placebo treatment groups in viral AUC from nasopharyngeal swabs
- The difference between VIS410 and placebo treatment groups in peak viral load and time to resolution of viral load from nasopharyngeal swabs
- Titer of anti-VIS410 antibody-positive samples

3.3 EXPLORATORY ENDPOINTS

- PK parameters (C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-last}, $t_{1/2}$) of VIS410 from nasopharyngeal secretions
- Genotypic and phenotypic assessment to determine the emergence of VIS410-resistant viruses
- Correlations between serum and/or nasopharyngeal PK with viral load, clinical symptoms, presence of ADAs, and additional endpoints
- Titer of anti-influenza A antibodies by hemagglutinin inhibition assay (HAI) in serum
- Correlations between virology and safety parameters and/or additional parameters may be explored

4. STUDY DESIGN

4.1 OVERVIEW OF STUDY DESIGN

This is a Phase 2a randomized, double-blind, placebo-controlled study to be conducted in approximately 150 subjects with uncomplicated influenza. This study will include approximately 50–75 clinical sites worldwide.

Subjects will be admitted to an infusion unit for drug administration and observation following infusion. The study is designed to compare an infusion of a single high or low IV

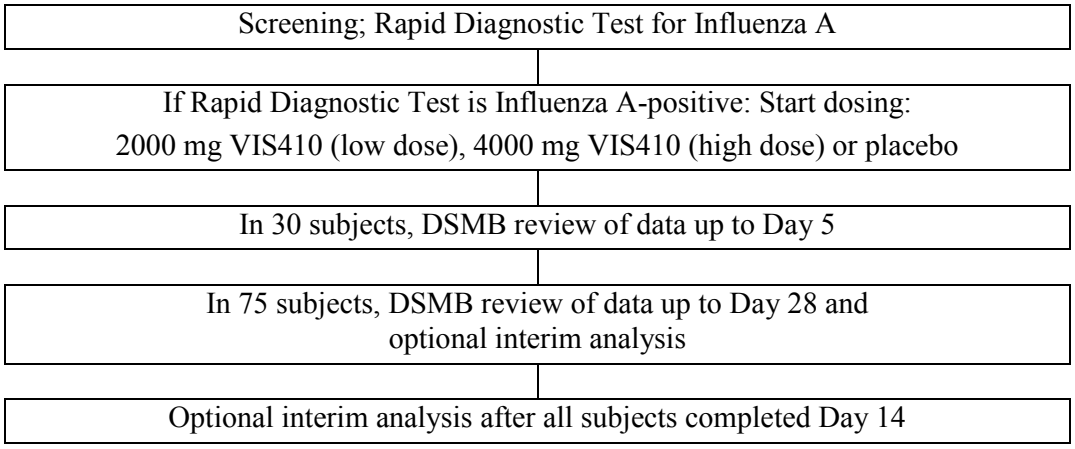
dose of VIS410 against placebo. Subjects will be assigned randomly to receive VIS410 at a dose of 2000 mg (low dose) or 4000 mg (high dose) or placebo (0.9% sodium chloride) at a ratio of 1:1:1 using a permuted block randomization method. Eligible subjects will receive VIS410 2000 mg, VIS410 4000 mg, or placebo administered as a single IV infusion over 2 hours on Day 1. Subjects will receive a pretreatment regimen of diphenhydramine 50 mg PO and ibuprofen 400 mg PO or acetylsalicylic acid 325 mg PO 60 minutes before infusion.

The subjects will be observed for at least 2 hours after the end of the infusion and will have a follow-up phone call in the evening of the dosing day to ensure subjects' safety and well-being. Subjects will return for follow-up visits on Days 3 (±1 day), 5 (±1 day), 7 (±1 day), 14 (±3 days), 28 (±3 days), 56 (±7 days) and 100 (±7 days). In addition, between clinic visits up to Day 7 (e.g., Days 2, 4 and 6) subjects will receive a follow-up telephone call to ensure compliance with FluPRO Influenza Symptom Questionnaire and review any new or worsening signs or symptoms. The Schedule of Assessments is presented in Table 1.

An independent Data Safety Monitoring Board (DSMB) will be established to review all available safety data after 30 subjects have completed the Day 5 visit and again after 75 subjects have completed the Day 28 visit. In addition, following the first DSMB, the DSMB will convene if the overall relative GI adverse event rate reaches 50% or the rate of moderate GI adverse events reaches 25%.

A schematic overview of the study design is shown in Figure 1. The assessments performed are summarized per visit in the Time and Events Schedule.

Figure 1. Schematic Overview of the Study



4.2 DISCUSSION OF STUDY DESIGN

Dose Selection

Various methods were utilized to determine the efficacious dose of VIS410 in humans for the treatment of influenza. These methods included evaluation of doses and exposures to provide VIS410 levels which exceed in vitro susceptibility measures, including neutralization EC_{50} and binding affinity, bridging efficacious doses in preclinical species to humans based on a mg/kg dose and PK, and exploratory PK/PD analyses of serum and nasal exposure versus antiviral activity of VIS410 in a human influenza virus challenge study. VIS410 broadly

neutralizes influenza A strains in vitro with EC_{50} values ranging from 0.03 to 64.2 µg/mL (median of 3.15 µg/mL) and binds with high avidity (30 to 380 picomolar) to HA across Group 1 and Group 2 subtypes. VIS410 doses of approximately 2300 mg will result in C_{max} serum level of 873 µg/mL, which is well above median EC_{50} of 3.15 µg/mL in serum and nasal cavity for the duration of viral shedding. Furthermore, in preclinical animal studies, VIS410 demonstrated efficacy at doses of 20 to 30 mg/kg or less against various Group 1 and Group 2 influenza A strains with EC_{50} values ranging from 0.57 to 2.4 µg/mL. Using a standard mg/kg conversion, these doses equate to 1500–2300 mg dose in humans (assuming a 75-kg subject). In a human influenza virus challenge study a single dose of 2300 mg demonstrated significant reduction in viral load area under the curve (AUC) and peak viral load compared with placebo, suggesting that doses of approximately 2300 mg may be efficacious in naturally occurring influenza infection. For strains with higher EC_{50}, doses greater than 2300 mg may be necessary to achieve adequate concentration at the primary site of infection. Based on these data, doses of 2000 and 4000 mg were selected for evaluation in this Phase 2a study. A dose of 4000 mg will ensure separation in VIS410 systemic exposures from the 2000 mg dose level to identify potential differences in safety and efficacy between the 2 doses. A dose level of 2000 mg provides a safety margin of approximately 9.4-fold to the nonclinical NOAEL (250 mg/kg), with the 4000 mg dose providing a safety margin of approximately 4.7-fold, assuming a 75-kg subject. In addition, in the Phase 1 pretreatment study (VIS410-102) doses of 2300 and 3800 mg were well tolerated following a pretreatment regimen of diphenhydramine plus ibuprofen.

Selection of Study Population

Approximately one hundred fifty (150) subjects will be enrolled in 3 equal arms: VIS410 2000 mg, VIS410 4000 mg, and placebo. The subjects will be carefully screened for eligibility.

4.3 INCLUSION CRITERIA

Subjects meeting all of the following criteria are eligible to participate in this study:

1) Male and female subjects aged ≥18 years and <65 years
2) Women should fulfill one of the following criteria:
   a) Post-menopausal; either amenorrhea ≥12 months or follicle stimulating hormone >40 mIU/mL as documented in their medical history.
   b) Surgically sterile; hysterectomy, bilateral oophorectomy, or tubal ligation.
   c) Women of childbearing potential participating in heterosexual sexual relations must be willing to use adequate contraception from screening until 60 days post-infusion, per Section 7.1.2.
3) Non-vasectomized (or vasectomized less than 6 months prior to dosing) male subjects who have a female partner of childbearing potential must use an effective birth control method (see Section 7.1.2) when having heterosexual intercourse, from screening until 60 days post-infusion.
4) Test positive for influenza A by Rapid Antigen Test performed with a commercially available test on an adequate nasopharyngeal specimen in accordance with the manufacturer's instructions

5) Presence of at least one respiratory symptom (cough, sore throat, or nasal symptoms) of moderate to severe intensity, or presence of at least one constitutional symptom (myalgia [aches and pains], headache, feverishness, or fatigue) of moderate to severe intensity
6) Onset of symptoms (time when the temperature was first measured as elevated [temperature of ≥100.4°F or ≥38°C], OR the time when the subject experienced at least one respiratory symptom or at least one constitutional symptom) no more than 72 hours before the start of infusion
7) Subject is able and willing to comply with study procedures, as per protocol
8) Subject is able and willing to give voluntary written informed consent

4.4 EXCLUSION CRITERIA

Subjects meeting any of the following criteria are excluded from participation in this study:

1) Use of NSAIDs or antihistamines within 6 hours of study drug dosing with the exception of those used as part of the pretreatment regimen.
2) History of intolerance or allergic response to monoclonal antibodies and/or pretreatment medications (diphenhydramine, ibuprofen and acetylsalicylic acid)
3) History of receiving monoclonal antibody products within 3 months prior to enrollment in this study or planned administration during the study period
4) Subjects in whom nasopharyngeal swabbing is not possible
5) Subject weight less than (<) 45 kg
6) Subjects with clinical history that would lead to increased risk of influenza complications including but not limited to clinically significant cardiac disease, moderate to severe asthma, or other moderate to severe chronic obstructive pulmonary disease, metabolic syndrome including moderate to severe diabetes or active tuberculosis.
7) History of chronic GI disease, including bleeding, ulceration, Irritable Bowel Syndrome, systemic mastocytosis, or chronic diarrhea
8) Women who are pregnant, breast-feeding, or considering becoming pregnant.
9) Patients with hypoxemia requiring oxygen support.
10) Clinical evidence of worsening of any chronic medical condition (temporally associated with the onset of symptoms of influenza) which, in the Investigator's opinion, indicates that such finding(s) could represent complications of influenza
11) Presence of immunocompromised status due to chronic illness, previous organ transplant, or use of immunosuppressive medical therapy including systemic steroids.
12) Presence of known human immunodeficiency virus (HIV) infection PLUS any one of the following:
    a) A CD4 count ≤500 cells/mm^3 (CD4 count obtained within the 3 months prior to screening)
    b) An Acquired Immune Deficiency Syndrome-defining illness. (HIV testing required at screening visit for all patients with no documented HIV status within 3 months prior to screening.)
13) Presence of known chronic hepatitis B or hepatitis C.
14) Receipt of any dose of antiviral therapy such as, but not limited to, rimantadine, amantadine, peramivir, zanamivir, laninamivir or oseltamivir in the 7 days prior to screening

15) Enrollment in any other investigational drug or device study, any disease or vaccine study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer
16) Presence of any pre-existing illness that, in the opinion of the Investigator, would place the subject at an unreasonably increased risk through participation in this study
17) Subjects unable to comply with study protocol procedures and study visit schedules for whatever reason
18) Subjects unable to take oral predose medication
19) Known or suspected alcohol or drug abuse, that is, abuse of a level that would compromise the safety or cooperation of the subject in the opinion of the Investigator
20) Subjects on chronic medications where the dose has not been stable for at least 3 months

5. TREATMENT(S)

Manufacturing, packaging, and labelling of the investigational product, VIS410, is done under the responsibility of the Sponsor.

5.1 PHYSICAL DESCRIPTION OF THE STUDY DRUG

The investigational product is manufactured by KBI Biopharma and Lyophilization Services of New England in accordance with Good Manufacturing Practice as required by the current Good Clinical Practice (GCP).

VIS410 is colorless to slightly yellow, clear to opalescent solution; essentially free of particles. VIS410 is formulated at a concentration of 25 mg/mL in 40 mM citrate-sodium phosphate, 150 mM sodium chloride, and 0.025% polysorbate 80.

The investigational product will be provided by the Sponsor. VIS410 will be supplied in Type I 20-mL glass vials containing a nominal 20 mL solution. A copy of the certificate of analysis of the investigational product will accompany the study drug to the clinical center.

The study drug will be labelled according to local law and regulatory requirements.

Specific dilution procedures of the study drug will be described in detail in the dispensing protocol.

Placebo will be a normal saline solution (0.9%) and will be prepared by the pharmacist.

5.2 OTHER MEDICATION ADMINISTERED IN THE STUDY

Chronic medications not listed in excluded concomitant medications, are permitted where the dose has been stable for at least 3 months prior to screening.

In case of hospitalization due to worsening of influenza symptoms, subjects should be managed per standard of care and local guidelines, which may include use of neuraminidase inhibitors.

Subjects will receive a pretreatment regimen of diphenhydramine 50 mg PO and either ibuprofen 400 mg PO or acetylsalicylic acid 325 mg PO 60 minutes before infusion. If the subject has any history of delayed gastric emptying, including premenstruation syndrome or menstruation, the subject may receive premedications 120 minutes prior to IV infusion.

5.3 STORAGE AND DRUG ACCOUNTABILITY

5.3.1 *Study Drug*

The Investigator (or designee) is responsible for the safe storage of all study drugs assigned to the clinical site. The investigational product should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the investigational product, and maintained within the appropriate ranges of temperature. All study drugs must be stored in the original packaging and as specified at delivery.

The study investigational product be stored between 2°C and 8°C and should be protected from light during storage at the clinical site.

Regular temperature recordings of the study drug storage refrigerator at the clinical site should be performed. In case a deviation in the storage conditions should occur, the site must not further dispense the affected study drug; instead, the Sponsor should be notified and will confirm whether or not the study drug may be further dispensed.

The Investigator is responsible for ensuring that all study drugs received at the clinical site are inventoried and accounted for throughout the study.

Study drugs should be dispensed under the supervision of the Investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. The Investigator must maintain accurate records demonstrating date and amount of drugs administered to whom and by whom. Study drugs will be supplied only to subjects participating in the study.

The Monitor responsible for drug accountability will periodically check the supplies of study drugs held by the Investigator or pharmacist to ensure accountability and appropriate storage conditions for all the study drugs held at the site.

Unused study drugs must be available for verification by the Sponsor's Monitor responsible for drug accountability during on-site monitoring visits. Any discrepancies between returned and expected returned study drugs should be explained.

After the last visit of the last subject in the study (LSLV), any used and unused investigational product will be returned to the Sponsor, or destroyed with the Sponsor's written permission (in this case a certificate of destruction will be provided and filed in the Trial Master File).

Hazardous materials such as used needles and syringes should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

5.4 DOSE AND ADMINISTRATION

The site's unblinded pharmacist or properly trained designee will prepare the VIS410 or placebo according to the instructions in the pharmacy manual. The required amount of VIS410 to be dosed (2000 mg or 4000 mg) will be diluted with normal saline up to a total volume of 200 mL. For placebo subjects, 200 mL of normal saline will be prepared.

The study infusion will be administered IV using a 0.22 µm in-line filter and will be controlled by a volumetric pump. Standard, uniform-length infusion lines will be used and

microfilters will be provided by the Sponsor. Length of IV line will be set for maximum volume of 25 mL. The infusion bag will be covered with an opaque sleeve in the pharmacy to maintain the study blind. The product will be administered IV at a rate of 100 mL/h, over 2 hours. After 200 mL of the diluted dose has been administered (the infusion bag is empty), the infusion line will be flushed with 25 mL of normal saline to ensure the total product dose is delivered. The infusion time may be longer at the Investigator's discretion based on local infusion site-related symptoms up to a maximum of 4 hours. VIS410 or placebo will be administered within 48 hours of being prepared by the study pharmacist. All doses of study drug will be administered in the clinic under the direct supervision of the Investigator or designee. Following administration, subjects will be observed for at least 2 hours at the infusion center and discharged if considered safe by the investigator. Prior to discharge, all subjects will be counseled on the potential GI AEs and management of these events.

Pretreatment: Subjects will be given a pretreatment regimen of diphenhydramine 50 mg PO with ibuprofen 400 mg PO or acetylsalicylic acid 325 mg PO 60 minutes before the IV infusion. If the subject has any history of delayed gastric emptying, including premenstruation syndrome or menstruation, they may receive premedications 120 minutes prior to IV infusion. In subjects with underlying renal impairment, caution should be taken with use of NSAIDs (ibuprofen or acetylsalicylic acid). Subjects with renal impairment must be adequately hydrated prior to administration of the pretreatment regimen and renal function should be monitored to ensure subject safety.

5.5 TREATMENT COMPLIANCE

To ensure treatment compliance, all study drug infusions will be supervised by the Investigator or his/her designee.

5.6 DATA SAFETY MONITORING BOARD

An independent DSMB will be established to review all available safety data after 30 subjects have completed the Day 5 visit and again after 75 subjects have completed the Day 28 visit. In addition, following the first DSMB, the DSMB will convene if the overall relative GI adverse event rate reaches 50% or the rate of moderate GI adverse events reaches 25%. Study enrollment and dosing will continue whilst the DSMB evaluates data.

Assessment of subject safety will be determined from vital sign measurements ECGs, physical examinations, hematology, chemistry and urinalysis laboratory testing, use of concomitant medications, and review of AEs should they occur.

If requested by the DSMB, additional meetings can be scheduled to follow up further safety data during the study. The DSMB will review the safety data in detail. If any safety concern is raised by the DSMB, treatment can be temporarily or permanently halted.

Doses may be adjusted downward at the discretion of the DSMB based on review of safety data including GI adverse events. Further details will be described in a separate DSMB charter.

6. PRIOR AND CONCOMITANT THERAPY

All therapies other than the study drug administered from signing of informed consent until the last study visit must be recorded in the electronic data capture (EDC) system (name of the drug and dates of administration). Intake of concomitant medication(s) will be monitored continuously from signing of Informed Consent Form (ICF) until the last study visit.

6.1 PRIOR MEDICATIONS

All medications the subject has taken within 14 days of study drug administration will be documented in the EDC. Influenza vaccination within the prior 6 months will also be documented in the EDC. The use of over the counter, symptom-modifying drugs such as NSAIDS, antihistamines, or pseudoephedrine are prohibited in the 6 hours prior to dosing of study drug with the exception of the pretreatment medications.

6.2 PERMITTED CONCOMITANT THERAPIES

The use of contraception and acetaminophen (paracetamol), as per license, is allowed during the study. As the impact of VIS410 on symptoms of influenza is a secondary objective of this study, the use of acetaminophen (paracetamol) should be minimized.

Chronic medications not listed in excluded concomitant medications, are permitted where the dose has been stable for at least 3 months prior to screening.

The use of symptom-modifying drugs such as NSAIDS, antihistamines, or pseudoephedrine are discouraged and in case a symptom modifying agent is needed, paracetamol/acetaminophen should be encouraged as the drug of choice.

In case of clinical worsening of influenza-related symptoms recorded at baseline or development of two new influenza-related symptoms 48 hours after study drug administration, additional antiviral prescription medication may be used, at the discretion of the Investigator, for management of influenza-like symptoms per standard of care. Investigator can decide to initiate antiviral therapy sooner as needed for subject safety and well-being.

6.3 EXCLUDED CONCOMITANT MEDICATIONS

Consistent with exclusion criteria, the use of antivirals should be excluded except as outlined in Section 6.2. Excluded antiviral medications include, but are not limited to: rimantadine, amantadine, peramivir, zanamivir, laninamivir or oseltamivir.

Use of antibiotics is discouraged unless there is a documented or suspected bacterial infection.

7. ASSESSMENTS

AEs and concomitant medications will be recorded from signing of the ICF to the subject's last visit.

7.1 TIMING OF ASSESSMENTS

If the following assessments are planned at the same time, the order of assessments should be as follows:

1) Influenza Patient Reported Outcomes questionnaire
2) Vital signs
3) Nasopharyngeal swab
4) Blood sampling

7.1.1 *Screening Examination and Eligibility Screening Form*

All subjects must provide written informed consent before any study specific assessments or procedures are performed.

Subjects will be assigned a unique screening number prior to Rapid Antigen Testing. Following confirmation of influenza A infection, subjects will be assessed for inclusion and exclusion criteria and those who fulfill all the inclusion and none of the exclusion criteria will be randomized into the study.

A screen failure log must be maintained by the Investigator for all entry criteria failures.

7.1.2 *Contraception Requirements*

All women of childbearing potential and all male subjects must practice effective contraception from screening until 60 days post-infusion. For the purposes of this study, women who do not meet one of the following criteria listed below are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Non-childbearing potential:
  - Post-menopausal: ≥12 months of natural (spontaneous) amenorrhea or
  - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy or
  - follicle stimulating hormone > 40 mIU/mL
  - hysterectomy
  - bilateral tubal ligation

Women of childbearing potential and all male subjects participating in heterosexual sexual relations must be willing to practice effective contraception from screening until 60 days post-infusion. For the purposes of the study, highly effective contraception is defined as:

- Combination of an established form of hormonal contraception (oral, injected, or implanted) or an intrauterine device or intrauterine system

and

- A physical barrier method of contraception with use of a spermicide such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide, unless not available in a country
- Male vasectomy with negative semen analysis documentation. The use of contraception does not apply if the male partner has been vasectomized at least 6 months prior to dosing
- Complete abstinence can be considered an acceptable method of contraception at the discretion of the Investigator. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not considered acceptable methods of contraception

The combination of 2 barrier methods, periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 10.8.

7.1.3 *Procedures for Enrollment of Eligible Subjects*

Once a subject has fulfilled the entry criteria, he/she will be assigned a unique identifier. The site will randomize the subject using the Interactive Web Response System (IWRS).

7.1.4 *Clinical Assessments and Procedures*

When required, subjects may be given a pre-screening informed consent in order to perform the Rapid Antigen Test for influenza. Flu-positive subjects will then be given a full explanation of the nature of the study and written informed consent (approved by the local ethics committee) will be obtained according to local requirements before any study-related assessment will be carried out.

At screening, subjects will be requested to attend the clinical center to have assessments performed as described in the Time and Events Schedule.

All results from the screening procedures required to evaluate eligibility must be available prior to drug infusion on Day 1. Any abnormal assessment at the screening visit will be assessed according to its clinical relevance, and if found relevant, the subject will not be included in the study.

On Day 1, eligibility of the subjects will be confirmed and assessments will be performed as described in the Time and Events Schedule.

Subjects will be admitted to the clinical center on Day 1 and will remain at the clinical center until at least 2 hours after study drug infusion on Day 1 and discharged if considered safe by the investigator. Prior to discharge, all subjects will be counseled on the potential GI AEs and management of these events. Subjects will have a follow-up phone call in the evening of the dosing day to ensure safety and well-being.

Follow-up Clinic Visits and Telephone Calls:

All subjects will be asked to come back to the clinical center for follow-up visits on Day 3 (±1 day), 5 (±1 day), 7 (±1 day), 14 (±3 days), 28 (±3 days), 56 (±7 days), and Day 100 (±7 days). In order to provide some flexibility for the subjects regarding the site visits and to maintain the integrity of the study design, a time window is permitted for the follow-up visits in case of time conflict or unforeseen circumstances.

In addition, between clinic visits up to Day 7 (e.g., Days 2, 4 and 6) subjects will receive a follow-up telephone call to ensure compliance with FluPRO Influenza Symptom Questionnaire and review any new or worsening signs or symptoms.

Subjects who terminate the study before completion of the scheduled study procedures for any reason (AE, withdrawal of consent, etc.) should be asked to complete study assessments (including safety) prior to withdrawal if possible. Subjects who withdraw for safety reasons should come for a safety follow-up visit as soon as possible within 14 days after discontinuation.

7.1.5 *Virological Assessments*

The virological laboratory assessments are:

- At screening, a single nasopharyngeal swab will be obtained from one nostril for the rapid test.
- A nasopharyngeal swab will be collected from each nostril as described in the schedule of assessments and laboratory manual. These swabs will be sent to a central virology laboratory for processing into appropriate aliquots for virology and analysis as detailed in Sections 7.2.1, 7.3.1, 7.4, and 7.5.
- Further details on sample collection, processing, shipment, and storage will be described in the laboratory manual.
- Virology samples taken from all subjects may be infectious and will be classified as “diagnostic specimens” for dispatch purposes.
- The Investigator may also perform additional tests in the local laboratory consistent with standard of care for the illness being treated.

7.1.6 *Unscheduled Visits*

Unscheduled visits can be planned at the discretion of the Investigator to obtain additional information to ensure the safety of the subject.

Subjects will be instructed to contact the trial center if they exhibit worsening symptoms or new episode of influenza-like illness so that they may be monitored and asked to return to the site for additional assessments (safety, nasopharyngeal swabbing) at the Investigator’s discretion. Findings made during unscheduled visits should be reported in the EDC system and should be reported in the source documents.

7.2 PHARMACOKINETIC EVALUATIONS

7.2.1 *Sample Collection and Handling*

Throughout the study, 5 mL venous blood samples will be collected for analysis of VIS410 in serum, according to the time points defined in the Time and Events Schedule. The exact date and time of blood sampling and of administration of the study drug must be recorded in the EDC system.

Blood samples will be collected by venipuncture or via indwelling cannula in the forearm into standard serum separator tubes and will be immediately chilled (ice bath). Further procedures for sample collection, shipment, processing, and storage will be described in the laboratory manual.

Nasopharyngeal swabs for determination of VIS410 concentration from nasopharyngeal secretions will be taken at the time points defined in the Time and Events Schedule. Further details on sample collection, processing, shipment, and storage will be described in the laboratory manual.

7.2.2 *Bioanalysis*

Serum samples and nasopharyngeal swabs for determination of the concentration of VIS410 will be analyzed under the responsibility of the Sponsor.

7.2.3 *Pharmacokinetic Parameters*

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 6.3 or higher) will be used to estimate PK parameters in serum and from nasopharyngeal secretions as described below.

The following PK parameters will be determined for VIS410 in serum and/or from nasopharyngeal secretions:

- C_{max}: maximum observed concentration
- T_{max}: time of C_{max}
- $AUC_{0-\infty}$: area under the concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-last}: area under the concentration-time curve from time 0 to the last measurable concentration
- $t_{1/2}$: terminal elimination half-life
- CL: total clearance (serum only)
- V_d: volume of distribution (serum only)
- Ratio of nasal:serum AUC

Additional PK parameters may be determined as appropriate. PK data from this study will be also analyzed by population PK modeling as appropriate.

7.3 ILLNESS EVALUATIONS

7.3.1 *Viral Shedding*

Nasopharyngeal swabs to determine viral shedding will be taken as indicated in the Time and Events Schedule. Further details on sample collection, processing, shipment, and storage will be described in the laboratory manual.

7.3.2 *Signs and Symptoms of Influenza*

The FluPRO questionnaire will be completed by the subject at the time points indicated in the Time and Events Schedule.

Unsolicited (i.e., not collected via the FluPRO questionnaire) signs and symptoms will be collected and scored via a targeted physical exam that will be performed by the Investigator or designee. Timing of this assessment is provided in the Time and Events Schedule and is to be performed at the discretion of the Investigator or designee.

Body temperature will also be measured. Fever is defined as a body temperature ≥38°C.

The solicited and unsolicited signs and symptoms of influenza will not be reported as AEs as these constitute an endpoint of the study and will be recorded as such, unless a situation arises whereby it is the opinion of the Investigator to do so.

7.4 IMMUNOLOGY

Blood samples for immunology assessments will be collected at the time points indicated in the Time and Events Schedule according to the instructions provided in the laboratory manual.

7.4.1 *ADA Response*

Throughout the study, 5 mL venous blood samples will be collected to determine anti-VIS410 antibody titers according to the time points defined in the Time and Events Schedule and according to the instructions provided in the laboratory manual. The exact date and time of blood sampling must be recorded in the EDC system. Anti-VIS410 antibody titers will be determined by Visterra or designee. These samples may be stored for further characterization of the effect of ADA on neutralization in accordance with local regulations.

7.4.2 *Anti-Influenza Antibody Response*

Venous serum samples (5 mL) will be collected to determine anti-influenza antibody titers according to the time points defined in the Time and Events Schedule and according to the instructions provided in the laboratory manual. Anti-influenza antibody titers will be determined by Visterra or designee.

7.5 RESISTANCE ANALYSIS

Analysis of resistance will be performed by Visterra or designee on selected samples from nasopharyngeal swabs. Further procedures for sample collection, processing, shipment, and storage will be described in the laboratory manual.

7.6 SAFETY EVALUATIONS

The safety assessment in this study will be based on AEs, clinical laboratory tests, vital signs, and physical examination, as described in the following sections.

7.6.1 *Adverse Events*

AEs will be monitored continuously from signing of informed consent until the last study-related activity. At regular intervals during the study, subjects will be asked non-leading questions to determine the occurrence of any AEs. All AEs reported spontaneously during the course of the study will be recorded as well.

Subjects will be observed during infusion and for at least 2 hours after completion of administration of study treatment to allow monitoring for possible hypersensitivity reactions, anaphylactic reactions, or other AEs that occur during this time period.

All AEs will be recorded in the EDC system, except for the symptoms of influenza collected via the FluPRO questionnaire as discussed in Section 7.3.2.

For detailed definitions and reporting procedures of AEs, see Section 10.

7.6.2 *Clinical Laboratory Tests*

Blood samples will be collected by venipuncture or via indwelling cannula at the time points indicated in the Time and Events Schedule.

Standard laboratory tests will be performed by a central or local laboratory. Appendix 1 lists the biochemistry, hematology, coagulation, and serology tests that will be performed on the safety blood samples.

Creatine kinase-MB, creatinine kinase, and troponin are to be measured in the case where the subject has chest pain.

A midstream urine sample will be collected for urinalysis by dipstick, flow cytometry, and microscopic examination. Appendix 1 lists the urinalysis parameters that will be assessed.

Urine pregnancy tests will be performed at the time points indicated in the Time and Events Schedule.

The Investigator must review the laboratory report, document this review, and record any change occurring during the study he/she considers to be clinically relevant in the EDC system. Laboratory values outside the normal range will be flagged and their clinical relevance will be assessed by the Investigator.

7.6.3 *Vital Signs*

Vital sign parameters will be assessed after 5 minutes in supine position at the time points indicated in the Time and Events Schedule. The vital sign parameters that will be assessed are supine systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate and body temperature.

Body temperature will be assessed using a thermometer preferably at approximately the same times of day for each measurement.

Any change from baseline in vital sign values occurring during the study that is considered to be clinically relevant by the Investigator should be recorded in the EDC system.

7.6.4 *Electrocardiography*

Single, 12-lead ECGs will be performed after a 5-minute rest at the time points indicated in the Time and Events Schedule. The ECG parameters assessed are heart rate, PR interval, QRS interval, QT interval. Values for QT corrected for heart rate (QTc) will be derived. QTc corrected according to Fridericia (QTcF) [6] will be the primary correction parameter. QTc parameters can be calculated subsequently if not immediately available at the site. If a subject has an elevated QTc >500 msec/min on assessment then repeat assessments in triplicate should be performed for confirmation.

Any change from baseline in ECG values occurring during the study that is considered to be clinically relevant by the Investigator should be recorded in the EDC system.

7.6.5 *Physical Examination*

A complete physical examination will be performed at the time points indicated in the Time and Events Schedule. A targeted physical exam may be performed at the Investigator's or his/her designee's discretion at the time points indicated in the Time and Events Schedule.

Physical examination at screening will include height and weight. To obtain the actual body weight, subjects must be weighed lightly clothed at screening. The height should be measured barefoot.

Any change in physical examination occurring during the study that is considered to be clinically relevant by the Investigator should be recorded in the EDC system.

7.7 TOTAL VOLUME OF BLOOD SAMPLING

The total volume of blood that will be drawn from each subject will be approximately 175 mL over the course of the study but no more than 25 mL per visit. In order to obtain additional information to ensure a subject's safety (i.e., an AE), additional blood samples (up to 50 mL) and/or urine samples may be taken at the discretion of the Investigator per standard of care.

7.8 APPROPRIATENESS OF MEASUREMENTS

The assessments that will be made in this study are standard, and are generally recognized as reliable, accurate, and relevant.

8. STUDY TERMINATION/COMPLETION

8.1 STUDY COMPLETION

A subject will be considered to have completed the study if he or she has completed the last follow-up visit (Day 100).

8.2 WITHDRAWAL OF SUBJECTS FROM STUDY

Subjects have the right to withdraw from the study at any time for any reason, including personal reasons. A subject can withdraw without giving a reason. The Investigator should, however, try to find out why a subject has withdrawn from the study and document the reason for withdrawal in the source documents and in the EDC system.

Subjects may withdraw from the study, or be withdrawn at the request of the Investigator or Sponsor (or designee). Each subject withdrawn from the study after receipt of any amount of study drug is to be encouraged to undergo as many post-study drug administration assessments as possible at the time of withdrawal. The reason for a subject's withdrawal should be recorded on the appropriate page(s) of the electronic Case Report Form. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent;
- Significant subject noncompliance, defined as refusal or inability to adhere to the protocol requirements, e.g., subject restrictions and follow-up visit schedule;
- The Investigator determines that it is in the best interest of the subject to withdraw from study participation

If a subject is withdrawn from the study as a result of a product-related SAE (for details on AE reporting see Section 10), notify the Study Monitor and Sponsor within 24 hours. If a subject is withdrawn from the study due to an AE that is possibly related to study drug, notify the Sponsor within 2 days from the event.

If there is a medical reason for withdrawal, the Investigator will monitor the subject until satisfactory health has returned.

Subjects who terminate the study before completion of the scheduled study procedures for any reason (AE, withdrawal of consent, etc.) should be asked to complete study assessments (including safety) prior to withdrawal if possible. Subjects who withdraw for safety reasons should come for a safety follow-up visit within 14 days after discontinuation.

Study drugs assigned to a withdrawn subject must not be assigned to another subject.

8.3 STOPPING RULES OR DISCONTINUATION CRITERIA

The study will be overseen by a DSMB (see Section 5.6). Based upon any safety assessments and after mutual agreement with the Investigator (or designee) and the Sponsor, the study may be temporarily or permanently halted. Study enrollment and dosing will continue whilst the DSMB evaluates data.

Dosing will temporarily pause whilst the DSMB meets if:

- a drug-related or unexpected drug-related SAE occurs in at least 1 subject,

- 25% or more subjects have GI symptoms of Grade 3 following the first DSMB.

Doses may be adjusted downward at the discretion of the DSMB based on review of safety data including GI adverse events.

9. STATISTICAL METHODS

9.1 DETERMINATION OF SAMPLE SIZE

The study will enroll approximately 150 subjects. No formal sample size calculations were done for this study. The sample size is consistent with Phase 2a studies to assess safety and tolerability.

9.2 RANDOMIZATION AND BLINDING

This will be a double-blind study. The Contract Research Organization (CRO) and site study personnel and Visterra personnel will not be aware of which treatment (active study drug or placebo) the subjects have been given. Subjects will not be aware of which treatment they have been administered.

Subjects will be randomized 1:1:1 to receive VIS410 2000 mg, VIS410 4000 mg, or placebo. A randomization list with randomization numbers will be created. The randomization numbers must be used sequentially to ensure an overall balance; no randomization number can be skipped. Allocation of each subject to a given treatment sequence will be described in a randomization list prepared by Visterra or designee. The randomization will be balanced using randomly permuted blocks across the treatment groups.

The randomization list will not be available to the subjects, Investigators, (blinded) monitors, or employees of the clinical center involved in the management of the study before unblinding of the data, unless in case of emergency. The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list. The CRO performing data management and statistical activities will receive a copy of the randomization list during database lock. Other team members will not have access to any data that could lead to unblinding.

Unblinding of the individual subject's treatment by the Investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the Investigator must first attempt to contact the Medical Monitor or appropriate back up (contact information as detailed in a separate document), to discuss and agree to the need for unblinding to occur. The Medical Monitor or designee will answer calls 24 hours a day, 7 days a week, 365 days of the year. In situations in which the Investigator has tried, but is unable to reach the Medical Monitor, they should use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Medical Monitor.

Once a subject's treatment assignment has been unblinded, the Medical Monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., reason and date) shall be clearly recorded in the subject's study file, as part of relevant standard operating procedures. In addition, the Investigator should consider whether the clinical event prompting unblinding should be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Visterra or designee.

Visterra or designee will also unblind any SAE reports that are serious, unexpected, and considered to be related to the study drug, in accordance with safety reporting guidance and regulations.

9.3 STATISTICAL ANALYSIS

VIS410 endpoints will compare aggregated VIS410 data as well as different dose levels of VIS410 to the placebo arm. Further details of the statistical methodology will be described in the statistical analysis plan (SAP).

9.3.1 *Analysis Populations*

The following analysis populations will be defined for the study:

Intent-to-Treat (ITT): All subjects randomized to treatment.
Modified Intent-to-Treat (mITT): All subjects who receive IV study drug and are confirmed influenza A positive by a molecular test at the central virological laboratory.
Safety Population: All ITT subjects who received IV study drug.
PK Population (PK): All subjects who received IV study drug with at least 1 PK parameter that can be calculated.

9.3.2 *Initial Characteristics of the Subject Sample*

Summary statistics will be provided per treatment group for demographic (e.g., age, height, weight, Body Mass Index, race, gender) and other initial subject characteristics (physical examination, medical history, concomitant diseases) will be provided per treatment group and for the total group. The ITT population will be used for the summaries.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

9.3.3 *Pharmacokinetics*

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 6.3 or higher) will be used to estimate the PK parameters in serum and nasopharyngeal secretions (see Section 7.2.3) described below. All calculations will use the actual times recorded in the EDC system for dosing and sampling. Individual and mean (±SD) or median concentrations versus time profiles will be plotted by study period on both linear and logarithmic scales. Additional plots and PK parameters may be generated as appropriate. The PK population will be used for the summaries.

Serum Pharmacokinetics

Serum concentrations and the computed PK parameters will be listed by subjects for VIS410. Summary statistics of serum concentrations and PK parameters will be presented including means, geometric means, standard deviations, CV, medians and ranges, as appropriate. Additional analyses and summaries may be generated as appropriate.

The following PK parameters will be determined for VIS410 in serum:

- C_{max}: maximum observed serum concentration
- T_{max}: time of C_{max}
- $AUC_{0-\infty}$: area under the serum concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-last}: area under the serum concentration-time curve from time 0 to the last measurable concentration
- $t_{1/2}$: terminal elimination half-life
- CL: total clearance
- V_d: volume of distribution

PK data from this study will be also analyzed by population PK modeling.

Nasopharyngeal Secretion Pharmacokinetics

Nasopharyngeal secretion concentrations and the computed PK parameters will be listed by subject for VIS410. Summary statistics of nasopharyngeal secretion concentrations and PK parameters will be presented including means, geometric means, standard deviations, CV, medians and ranges, as appropriate. Additional analyses and summaries may be generated as appropriate.

The following PK parameters will be determined for VIS410 from nasopharyngeal secretions:

- C_{max}: maximum concentration observed from nasopharyngeal secretions
- T_{max}: time of C_{max}
- $AUC_{0-\infty}$: area under the nasopharyngeal secretion concentration-time curve from time 0 extrapolated to infinity
- AUC_{0-last}: area under the nasopharyngeal secretion concentration-time curve from time 0 to the last measurable concentration
- $t_{1/2}$: terminal elimination half-life
- Ratio of nasal:serum AUC

Additional PK parameters may be determined as appropriate.

9.3.4 *Viral Shedding*

Additional sensitivity analysis may be conducted excluding subjects that received concomitant antiviral therapy during the course of the study.

- One-way analysis of variance (ANOVA) (with treatment group as the factor) or other appropriate statistics detailed in the SAP to assess the difference between VIS410 treatment groups vs placebo in the area under the viral load-time curve (AUC) for influenza virus based on quantification of viral load from nasal swabs

- Descriptive statistics of the area under the viral load-time curve (AUC) for influenza virus based on quantification of viral load from nasopharyngeal swabs by treatment group.
- Descriptive statistics of the time to resolution of viral load and of the peak viral load by treatment group.

The mITT population will be used for the summaries.

9.3.5 *Signs and Symptoms of Influenza*

The difference between VIS410 and placebo will be assessed as outlined below.

- Frequency tabulation of the occurrence and severity of each of the subject-reported symptoms of influenza-like illness by assessment time point and by treatment group
- Descriptive statistics of the duration of each of the subject-reported symptoms of influenza-like illness by treatment group

Additional sensitivity analysis may be conducted excluding subjects that received concomitant antiviral therapy during the course of the study. The mITT population will be used for the summaries. Additional populations may be analyzed as described in the SAP.

9.3.6 *Immunology*

Immunological assessments will be summarized by parameter, treatment group, and time point using descriptive statistics:

- Anti-VIS410 antibody titers by ADA in serum
- Anti-influenza A antibodies by HAI in serum
- HAI levels to determine a proper immune response to the influenza infection

The mITT population will be used for the summaries. Additional populations may be analyzed as described in the SAP.

Anti-Drug Antibodies

Anti-VIS410 antibody titer will be summarized by treatment group and by time point using descriptive statistics.

9.3.7 *Exploratory Pharmacokinetic/Pharmacodynamic Analyses*

Various techniques will be used to explore exposure-response relationships, and to compare the strength of the relationship between each independent variable (e.g., AUC, C_{max}, and concentration at specific time point) and the dependent variables (e.g., viral AUC, peak viral load, and time to cessation of viral shedding, clinical symptoms, and additional endpoints). These techniques may include graphical and statistical methods, including the creation of boxplots, spaghetti plots, histograms, and a variety of linear, nonlinear, or logistic regression techniques and time-to-event methods. If appropriate, continuous independent variables will be evaluated as such, and as categorical variables (grouping subjects into exposure categories).

9.3.8 *Safety*

The ITT, and safety populations will be used for the safety summaries. Additional populations may be analyzed and this will be documented in the SAP.

Adverse Events

The original terms in the EDC system by Investigators to identify AEs other than symptoms of influenza A will be fully described and coded according to the Medical Dictionary for Regulatory Activities (MedDRA current version 19). The reported AEs will be allocated to phases based on their start date. All AEs will be listed. All AEs with onset during the treatment phase (TEAEs) will be summarized.

AEs will be summarized by treatment group and by MedDRA body organ system and preferred term, severity, relatedness, and seriousness. Classical symptoms of influenza including cough, sore throat, nasal congestion, fatigue, headache, myalgia or low-grade fever should not be reported as AEs unless there is a relationship between the event and study medication.

The difference in proportions of subjects with AEs, TEAEs, AESIs, and SAEs between treatment groups and their 95% CI will be calculated (primary safety endpoint).

Special attention will be paid to those subjects who died, discontinued the study drug due to an AE, or experienced a severe or serious AE. Summaries, listings, and narratives (also see Section 12.11) may be provided, as appropriate.

Injection Site Tolerability

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

Complications of Influenza

Complications of influenza are defined as pneumonia, myocarditis, worsening of chronic bronchitis, other chronic pulmonary diseases, otitis, sinusitis, and death. Complications of influenza will be reported by variable, treatment group, and time point.

Clinical Laboratory Tests

Actual values and changes from baseline of each continuous biochemistry, hematology and urinalysis test will be evaluated using descriptive statistics by assessment time point and by treatment group. For categorical urinalysis tests, frequency tables of actual values will be provided by assessment time point and by treatment group.

Relative changes in clinical laboratory test values compared with values at baseline will be evaluated in according to the Division of Microbiology and Infectious Diseases (DMID) grading table or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined. A shift from baseline table of abnormalities in clinical laboratory test parameters will be provided by assessment time point and by treatment group.

A listing of subjects with any clinical laboratory test result outside the reference ranges will be provided.

Vital Signs

Actual values and changes from baseline of heart rate, respiratory rate, temperature, SBP, and DBP measurements will be evaluated by means of descriptive statistics by assessment time point and by treatment group.

A shift from baseline table of vital sign abnormalities will be provided by assessment time point and by treatment group.

Electrocardiography

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, and QT interval. Values for QT corrected for heart rate (QTc) will be derived. QTc corrected according to Fridericia (QTcF) [6] will be the primary correction parameter.

Actual values and changes from baseline of ECG variables will be evaluated by means of descriptive statistics by assessment time point and by treatment group.

A shift from baseline table of ECG abnormalities will be provided by assessment time point and by treatment group. For absolute QTcF interval prolongation (>450, >480, >500 msec) and changes from baseline (increase >30 and >60 msec), a frequency table by assessment time point and by treatment group will be provided.

Physical Examination

Abnormal findings in physical examination will be listed.

9.4 INTERIM ANALYSIS

The following optional safety and efficacy interim analyses may be performed at the following times:

- After 75 subjects have completed the Day 28 visit
- After all enrolled subjects have completed the Day 14 visit

The optional interim analysis would review safety and efficacy results in a partially blinded fashion. If performed, the interim analyses will be included in the SAP and will be used to assist with the planning of future studies. The statistician performing the analysis and the PK/PD team at Visterra may be unblinded.

10. ADVERSE EVENT REPORTING

10.1 DEFINITIONS

Type of Event	Collection Period
AESIs [a]	28 days after drug administration
TEAEs	Entire study period [b]
SAEs [c] and Pregnancies	Entire study period [b, d]

[a] If a subject was enrolled with a concurrent AESI, received investigational product, and then has worsening of an AESI (severity of symptoms), then this event should also be reported.
[b] The entire study period is from the time a subject receives the study drug through the Day 100 Visit.
[c] If the Investigator becomes aware of any related SAE after completion of the study, he or she is obligated to report this event.
[d] If a subject or the female partner of a male subject, becomes pregnant during the study or within 100 days following study drug infusion, the Sponsor must be notified within 24 hours of the site's knowledge of the pregnancy; the subject or partner will be followed until the end of the pregnancy; and the infant will be followed for 1 year after the birth, provided informed consent is obtained.

Adverse Event

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

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including clinical laboratory test abnormalities.

New or worsening symptoms of influenza including cough, sore throat, nasal congestion, fatigue, headache, myalgia or low-grade fever should not be reported as AEs unless they result in an SAE (i.e., lead to hospitalization).

Adverse Event of Special Interest

An AESI (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 Investigator to the Sponsor will be warranted. 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 trial Sponsor to other parties (e.g., regulators) might also be warranted (based on CIOMS VI).

For VIS410, the AESIs include the following:

- Abdominal cramping
- Diarrhea
- Nausea and vomiting
- Pruritus
- Rash

- Hypotension
- Throat tightening
- Trouble breathing or wheezing

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death
- is life-threatening, i.e., the patient was at risk of death at the time of the event (e.g., ventricular fibrillation and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization: Hospitalization refers to an overnight admission into hospital for the purpose of investigating and/or treating the AE. Hospitalization for an elective procedure, or routinely scheduled treatment for a pre-existing condition that has not worsened, is not an SAE.
- results in persistent or significant disability/incapacity, i.e., causing substantial disruption of the patient's ability to conduct normal life
- is a congenital anomaly/birth defect
- is medically significant, i.e., may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient's health or may require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Unlisted (Unexpected) Adverse Event

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information (Investigator Brochure [5]).

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Sponsor to be related to the study treatment administered.

The Sponsor or designee will report SUSARs and other applicable SAEs to the appropriate regulatory authorities, Central Institutional Review Board (IRBs)/Ethics Committees (ECs) and Investigators as required, according to local law.

Treatment-Emergent Adverse Event

A TEAE is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

10.2 INTENSITY OF ADVERSE EVENTS

Each AE must be rated on a 3-point scale of increasing intensity according to DMID (Appendix 2):

Note: the semi-colon within the description of the grade indicates 'or'.

Grade 1 Mild transient or mild discomfort (<48 hours); no medical intervention/therapy required

Grade 2 Moderate/mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 Severe/marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

10.3 CAUSALITY ASSESSMENT

The following binary choice will be used by the Investigator to describe the causality assessment with the test treatment:

Reasonable Possibility

There is evidence to suggest a causal relationship between the test treatment and the AE (e.g., AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure).

No Reasonable Possibility

There is no evidence to suggest a causal relationship between the test treatment and the AE.

10.4 ACTION TAKEN REGARDING INVESTIGATIONAL PRODUCT

The action taken towards the study drug must be described as follows:

- Permanently discontinued
- Stopped temporarily
- Modified infusion rate
- No action Taken
- Not applicable

10.5 OUTCOME

The outcome of each AE must be rated as follows:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown

10.6 RECORDING OF ADVERSE EVENTS

All (S)AEs occurring during the clinical investigation must be documented in the EDC system.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., skin erythema, induration, edema and warmth should be reported as "cellulitis"). Investigators must record their opinion concerning the relationship of the (S)AE to the study drug in the EDC system. All measures required for (S)AE management must be recorded in the source documents and reported according to Sponsor's instructions.

All (S)AEs occurring at any time during the study (including the follow-up period) will be followed by the Investigator until satisfactory resolution (e.g., value back to baseline value) or stabilization or until final database lock. If necessary, in order to obtain additional information to ensure safety to the subject, additional blood and urine samples may be taken at the discretion of the Investigator. Certain long-term AEs related to therapy cannot be followed until resolution within the setting of this study. In these cases follow up will be the responsibility of the treating physician.

10.7 REPORTING OF SERIOUS ADVERSE EVENTS

All SAEs, irrespective of the circumstances or suspected cause, must be reported on a Serious Adverse Event Form by the Investigator to the Sponsor or designee within 24 hours of their knowledge of the event, preferably by email. Other means of transmission can be decided when email is not possible (fax).

The Sponsor and Medical Monitor will be notified of SAEs within 24 hours.

Contact details for reporting SAEs:

Contact details for Pharm-Olam Medical Monitor:

The SAE form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

Follow-up and outcomes should be reported for all subjects that experience an SAE.

It is critical that the information provided on the Serious Adverse Event Form matches the information recorded in the EDC system for the same event. In addition, the same information is to be recorded in the source documents.

Copies of additional reports and documents should be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to CRO until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

10.8 PREGNANCY

Subjects should not become pregnant during the study.

The Investigator must report any pregnancy which occurs in a female subject or the female partner of a male subject up to 60 days after dosing by faxing the pregnancy form to the Sponsor or designee within 24 hours of the study site staff becoming aware of the pregnancy. The Investigator or study site staff must report the outcome of the pregnancy to the Sponsor or designee.

Contact details:

Pregnancy is not an SAE, however congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if the subject was pregnant during the study treatment period or in the 60-day period after dosing of study drug.

10.9 REPORTING OF SAES TO COMPETENT AUTHORITIES/ETHICS COMMITTEES

Visterra or designee is responsible for appropriate reporting of AEs to the regulatory authorities. Visterra or designee will also report to the Investigator all SAEs that are unlisted (unexpected) and associated with the use of the drug. The Investigator must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol, unless otherwise required and documented by the IEC/IRB.

Visterra or designee, will be responsible for unblinding and submitting SUSARs involving the study drug to the applicable regulatory authorities according to International Conference on Harmonization (ICH) guidelines. In addition, Visterra or designee, will be responsible for the submission of safety letters to the central IRB/EC and to participating Investigators of all SUSARs involving VIS410 according to applicable regulations. For clinical sites that use a local IRB/EC, it is the responsibility of the Investigator to promptly notify the local IRB/EC of all unexpected serious adverse drug reactions involving risk to human subjects.

After termination of the clinical study (determined as LSLV), any unexpected safety issue that changes the risk–benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the CRO as soon as possible to the competent authority(ies) concerned together with proposed actions.

11. ETHICAL ASPECTS

11.1 STUDY-SPECIFIC DESIGN CONSIDERATIONS

Potential subjects will be fully informed of the risks and requirements of the study and during the study, subjects will be provided with any new information that may affect their decision to continue participation. Subjects will be informed that their consent to participate in the study is voluntary and may be withdrawn at any time without the need to provide a reason and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

11.2 REGULATORY ETHICS COMPLIANCE

11.2.1 *Investigator Responsibilities*

The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the IRB/IEC, and/or the regulatory authority(ies).

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki; and that the clinical study data are credible.

11.2.2 *Independent Ethics Committee or Institutional Review Board*

An IRB/IEC should safeguard the rights, safety, and well-being of all study subjects. Special attention should be paid to studies that may include vulnerable subjects.

Before the start of the study, the Investigator (or Sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any updates) and any other written materials to be provided to the subjects;
- Sponsor-approved subject recruiting materials
- Investigator Brochure (or equivalent information) and addenda
- available safety information
- information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's current curriculum vitae or other documentation evidencing qualifications (unless not required, as documented by IEC/IRB)
- information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects;
- any other documents that the IEC/IRB may require to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full written approval of the final protocol and amendments (if any), the ICF(s) and updates (if any), applicable recruiting materials, and any other written information to be provided to the subjects, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the Investigator (or Sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- protocol amendments
- revision(s) to ICF and any other written materials to be provided to subjects;
- if applicable, new or revised subject recruiting materials approved by the Sponsor;
- revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's Brochure addenda or new edition(s)
- summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- reports of AEs that are serious, unlisted, and associated with the investigational drug
- new information that may adversely affect the safety of the subjects or the conduct of the study
- deviations from or changes to the protocol to eliminate immediate hazards to the subjects;
- report of deaths of subjects under the Investigator's care
- notification if a new Investigator is responsible for the study at the site
- Development Safety Update Report, Short Term Study Specific Safety Summary and Line Listings, where applicable
- any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the study subjects. If a deviation from, or a change to the protocol was implemented to eliminate an immediate hazard to study subjects, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IEC/IRB as soon as possible.

The Investigator (or Sponsor where required) will notify the IEC/IRB about the study completion within 90 days after the end of the study (defined as LSLV).

11.2.3 *Informed Consent*

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the investigational staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may refuse to participate or withdraw consent to participate at any time, without penalty or loss of benefits to which the subject was entitled. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The language used in the oral and written information about the study, including the ICF, should be non-technical and practical and should be understandable to the subject or the subject's legal representative. The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained, if permitted by local law.

11.2.4 *Privacy of Personal Data*

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his or her original medical

records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

12. ADMINISTRATIVE REQUIREMENTS

12.1 PROTOCOL AMENDMENTS

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the Sponsor, and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case an amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to the Sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

12.2 SUBJECT IDENTIFICATION, ENROLLMENT, AND SCREENING LOGS

The Investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and/or assigned number only.

The Investigator must also complete a subject-screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

12.3 SOURCE DOCUMENTATION

The EDC system is an electronic data capturing and information management system that will also serve as the data management system for this study. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based, will be collected in the EDC. The responsible study Monitor will check data at the monitoring visits to the clinical study site. The Investigator will ensure that the data collected are accurate, complete, and legible. Data will be monitored within EDC by the study Monitor who has only reading rights. Any changes required following monitoring will be made by site personnel or the Investigator and will be documented with a full audit trail within EDC.

At a minimum, source documentation must be available for the following: subject identification, eligibility, and study identification; date of informed consent, dates of visits, results of safety and efficacy parameters as required by the protocol, record of all AEs, follow up of AEs, concomitant medication, drug receipt/dispensing/return records, study drug

administration information, laboratory printouts (if not available digitally), date of study completion, and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the (e-)source documents be identifiable.

Source data may be directly captured from devices, transferred from third parties (e.g., laboratory data), or entered manually into the EDC system in use at the clinical center. In such case, the majority of the source data will only be available electronically. The remainder of the data, captured initially on paper, may be entered retrospectively into the EDC system.

Following the ICH/GCP guidelines, direct access to (e-)source documentation (medical records) must be allowed.

12.4 CASE REPORT FORM COMPLETION

All source data, except those that are paper based, will be collected directly into the EDC system. Paper-based sources will be manually transcribed in the EDC system. All data captured in EDC will be transferred to the clinical database electronically.

12.5 MONITORING

The monitoring of the study will be done under the responsibility of the Sponsor by the CRO.

The Monitor will perform on-site or remote monitoring visits as frequently as necessary. The Monitor will record dates of the on-site visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the Monitor will compare the data captured in the EDC system for completeness and accuracy and perform source data verification to any data that has been captured as paper source or entered in the system later on. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the EDC system are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site contact(s). If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to (e-)source documentation (medical records) must be allowed at all times for the purpose of verifying that the data recorded EDC system are consistent with the original (e-)source data. Findings from this review of captured data will be discussed with the investigational staff. During on-site monitoring visits (notified and agreed upfront with the investigational staff), the relevant investigational staff will be available, the (e-)source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The Monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

12.6 DATA MANAGEMENT

Data management of the study will be performed under the responsibility of the Sponsor by the CRO.

After the data are released by the Investigator and the Monitor has reviewed the data for completeness and accuracy, the data will be uploaded into the clinical database to perform cleaning activities. Only the data of randomized subjects will be captured in the clinical database.

Computerized data cleaning checks will be used in addition to manual review including listings review, to check for discrepancies and to ensure consistency and completeness of the data. Queries emerging during data cleaning will be generated by the clinical data manager in the EDC system. The Investigator or his designee will answer the queries and update the source data, if needed. Any changes required are to be documented with a full audit trail within the EDC system.

An interim lock of the database will occur at the time of the interim analysis (see Section 9.4).

The final clinical database will be locked as soon as it is considered clean. Only authorized and well-documented updates to the study data are possible after final database lock. The locked final database is used in the final statistical analysis for study reporting. Measures will be undertaken to protect subject data handed over by the Investigator to the Data Management Department and during inspections against disclosure to unauthorized third parties. Subject confidentiality will be maintained at all times.

12.7 DATA QUALITY ASSURANCE

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and by periodic monitoring visits by the Sponsor or designee.

Written instructions will be provided for the collection, preparation, and shipment of samples.

The Sponsor or its designee will review the EDC system for accuracy and completeness during (on-site) monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After upload of the data into the clinical study database, they will be verified for accuracy.

In accordance with Good Clinical Research Practice Guidelines and Recommendations, 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 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 agency concerning an upcoming inspection.

12.8 ON-SITE AUDITS

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, government or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

Similar procedures may also be conducted by agents of any regulatory body, either as part of 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 agency concerning an upcoming inspection.

12.9 STUDY TERMINATION

The Sponsor reserves the right to terminate the study at any time. In case of an early termination of the study for safety reasons, or temporary halt by the Sponsor, the IEC/IRB should be notified within 15 calendar days, including a detailed written explanation of the reasons for the termination/halt.

The end-of-study declaration will be submitted to the regulatory authorities and IEC after the complete study has ended. This notification will also be submitted within 90 days of the end of the study.

12.10 RECORD RETENTION

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain an archived copy of the EDC data and all paper source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

12.11 USE OF INFORMATION AND PUBLICATION

All information, including but not limited to information regarding VIS410 or the Sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data,

prior clinical data, formulation information) supplied by the Sponsor to the Investigator and not previously published, and any data generated as a result of this study are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the Sponsor's prior written consent.

The Investigator understands that the information developed in this clinical study will be used by the Sponsor in connection with the continued development of the study drug, and thus may be disclosed as required to other clinical Investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report written by the CRO under responsibility of the Sponsor and will contain EDC system data from all investigational sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator.

Clinical narratives will be written for the following events:

- All deaths (irrespective of drug relationship)
- All other SAEs during treatment with the study drug
- All discontinuations of the study due to AEs related to the study drug
- At the discretion of the team and after statistical analysis of the data, certain discontinuations not related to AEs or treatment failure, i.e., related to lost to follow up or withdrawal of consent (irrespective of treatment group)
- Any events of special interest explicitly requested by the regulatory agencies

A summary of this final version will be provided to the Investigators, to the applicable regulatory authorities, and IECs/IRBs, if required by the applicable regulatory requirements, within 1 year of the end of the study (Last Subject Last Visit).

The Sponsor shall have the right to publish such data and information without approval from the Investigator.

Individual site publications are not expected as individual sites may not recruit enough subjects to enable detailed publications; therefore, results of this study will be reported in total.

If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content and does not have the right to suppress information. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the

design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

12.12 REGISTRATION OF CLINICAL STUDIES AND DISCLOSURE OF RESULTS

The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

12.13 CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without Sponsor's written permission.

The Investigator must assure that subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, addresses, and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from the Sponsor.

13. REFERENCES

1. Treanor JJ, Hayden FG, Vrooman PS, et al, Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA. 2000;283(8):1016–024.
2. Schanzer DL, Langley JM, Tam TW. Co-morbidities associated with influenza-attributed mortality, 1994-2000, Canada. Vaccine. 2008;26(36):4697–703.
3. CDC. Estimates of deaths associated with seasonal influenza US, 1976-2007. MMWR. 2012;59(33):1057–62.
4. Babcock G, Szretter K, Sloan S, et al. VIS410, a broadly HA-targeting human antibody, neutralizes H5 and H7 isolates with pandemic potential. ICAAC, Denver, 2013.
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6. Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of subjects with heart disease. Acta Medica Scandinavica. 1920;53:469–86.
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APPENDIX 1: LABORATORY ASSESSMENTS

Urinalysis	Hematology	Chemistry
Dipstick: • Specific gravity • pH • Glucose • Protein • Blood • Ketones • Bilirubin • Urobilinogen • Nitrite • Leukocyte esterase Urine sedimentation count: • Erythrocytes (RBC) • Leukocytes (WBC) • Epithelial cells Microscopy • Crystals • Casts • Bacteria	Hemoglobin Hematocrit Red blood cells (RBC) White blood cells (WBC) with differential Lymphocytes Monocytes Neutrophils [c] Eosinophils Basophils Platelets	Albumin Alkaline phosphate Alanine amino transferase Aspartate amino transferase Bicarbonate Total bilirubin Direct bilirubin [b] Blood urea nitrogen (or urea) Calcium Chloride Creatinine Glucose [a] Lactate dehydrogenase Phosphate, inorganic Potassium Total protein Sodium Creatine kinase-MB [d], creatinine kinase [d], troponin [d]
Serology [a]	**Other Assessments**	**Coagulation**
Antibody screening test (immunoassay), rapid HIV test	Urine pregnancy test	Partial thromboplastin time Activated partial thromboplastin time

a Screening only
b Assay if total bilirubin is above normal range.
c If immature neutrophils are detected, the sample is to be flagged and a blood slide for microscopic analysis will be made. If Bands are detected in the microscopic analysis, then a result will be provided.
d Only measure if subject has chest pain.

APPENDIX 2: DMID ADULT TOXICITY TABLE

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
R_x = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 **Mild** Transient or mild discomfort (< 48 hours); no medical intervention/therapy required

GRADE 2 **Moderate** Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 **Severe** Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 **Life-threatening** Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, NCI's Common Toxicity Criteria (CTC), and World Health Organization (WHO)) have been adapted for use by the DMID and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 - 10.5 g/dL	8.0 - 9.4gm/dL	6.5 - 7.9 g/dL	< 6.5 g/dL
Absolute Neutrophil Count	1000-1500/ mm3	750-999/ mm3	500-749/ mm^3	<500/ mm^3
Platelets	75,000-99,999/ mm^3	50,000-74,999/ mm^3	20,000-49,999/ mm^3	<20,000/ mm^3
WBCs	11,000-13,000/mm^3	13,000-15,000/mm^3	15,000-30,000/ mm^3	>30,000 or <1,000/mm^3
% Polymorphonuclear Leucocytes + Band Cells	> 80%	90 – 95%	>95%	----------
Abnormal Fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: < 50 mg/dL ----------	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20-40 mcg/ mL	41-50 mcg/ mL	51-60 mcg/ mL	> 60 mcg/ mL
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	> 3 x ULN
Methemoglobin	5.0 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20.0 %

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/ L	123-129 mEq/ L	116-122 mEq/ L	< 116 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/ L	2.5 - 2.9 mEq/ L	2.0 - 2.4 mEq/ L or intensive replacement therapy or hospitalization required	< 2.0 mEq/ L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/L	> 7.0 mEq/ L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or abnormal calcium *with* life threatening arrhythmia or tetany

CHEMISTRIES (continued)				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6-12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 - 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or dialysis required

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 - <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Lipase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg - 1 g loss/day	2-3+ or 1- 2 g loss/day	4+ or 2-3.5 g loss/day	nephrotic syndrome or >3.5 g loss/day
Hematuria	microscopic only <10 RBC/HPF	gross, no clots >10 RBC/HPF	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase >20 mm/ Hg; no treatment	recurrent, chronic increase > 20mm/ Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, No treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral flu id treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/ moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% - 80% FEV_1 of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 50%-70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring Oxygen therapy

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV flu ids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	Requiring laxatives	Obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last <1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2 L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids

NEUROLOGICAL				
	Grade 1	Grade 2	Grade 3	Grade 4
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	Moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELATEL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	myalgia with no limitation of activity	Muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	Frank myonecrosis

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation or mist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, mutiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15-30 mm	>30mm	
Erythema	< 15mm	15-30 mm	>30mm	
Edema	< 15mm	15-30 mm	>30mm	
Rash at Injection Site	< 15mm	15-30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25-50% > 48 hours	normal activity decreased > 50% can't work	unable to care for self