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STATISTICAL ANALYSIS PLAN

PROTOCOL 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
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LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the serum concentration-time curve, time 0 to infinity
AUC_{0-last}	Area under the serum concentration-time curve, time 0 to the last measurable concentration
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CL	Total clearance
C_{max}	Maximum observed serum concentration
CV	Coefficient of Variance
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
FluPRO	Influenza Patient Reported Outcomes
HAI	Hemagglutinin inhibition assay
ICH	International Conference on Harmonization
LOCF	Last Observable Measurement Carried Forward
ITT	Intent-to-Treat

MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PCS	Potentially Clinically Significant
PK	Pharmacokinetics
PT	Preferred Term
QTcF	QT interval, using Fridericia's correction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
$T_{1/2}$	Terminal elimination half-life
TEAE	Treatment Emergent AE
T_{max}	Time of C_{max}
V_d	Volume distribution
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Visterra Inc. 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.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: E9 Guidance on Statistical Principles in Clinical Trials.

A kineticist will derive standard non-compartmental pharmacokinetics (PK) parameters. Their analysis will be described within this SAP, see Sec. 11. Any other PK/PD analyses, including population PK modeling, are beyond the scope of this document.

This SAP is based on the protocol Version 1.1 dated 14 September, 2016 and electronic Case Report Form (eCRF) version 2.0 dated 01 December 2016. In the event of future amendments to the protocol, or changes in the eCRFs, this SAP will be modified as necessary to account for changes relevant to the statistical analysis.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

2.1.1 Primary Objectives

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

2.1.2 Secondary Objectives

- Evaluate the efficacy of 2 dose levels of VIS410 compared with placebo on the time to alleviation of clinical symptoms of acute uncomplicated influenza
- Evaluate the effect of 2 dose levels of VIS410 on severity of influenza infection
- Assess the pharmacokinetics of 2 dose levels of VIS410 in serum
- Assess the effects of 2 dose levels of VIS410 on viral shedding
- Assess the immunogenicity of 2 dose levels of VIS410

2.1.3 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

2.2 Trial Design

This is a Phase 2a randomized, double-blind, placebo-controlled study to be conducted in approximately 150 subjects with uncomplicated influenza. The study is designed to compare an

infusion of a single high (4000 mg) or low (2000 mg) IV dose of VIS410 against placebo (0.9% sodium chloride). Subjects will be assigned randomly in a ratio of 1:1:1. 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 diphenhydramine 50 mg PO and acetylsalicylic acid 325 mg PO 60 minutes before infusion.

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 the Influenza Patient Reported Outcomes (FluPRO) Influenza Symptom Questionnaire and review any new or worsening signs or symptoms.

2.3 Primary Hypothesis

The primary objective is to assess the safety and tolerability of a single IV dose of VIS410 in subjects with uncomplicated influenza infection. There is no formal statistical testing for this protocol; differences between the treatments will be evaluated with 95% exact confidence intervals (CI) of the incidences of treatment-emergent AEs (TEAEs).

2.4 Study 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.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

- The proportion of subjects with adverse events (AEs) and serious AEs (SAEs) following administration of VIS410
- The proportion of subjects with TEAEs including
  - Hypersensitivity reaction
  - Anaphylactic reaction
  - 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 FluPRO 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}, $t_{1/2}$, AUC ratio for nasopharyngeal: serum) 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 GENERAL ANALYSIS DEFINITION

4.1 General Considerations

All statistical analyses and summary information are to be generated according to this SAP. Any deviations from this SAP will be documented in the CSR.

These descriptive statistics will be presented for continuous parameters: the number of subjects used in the calculation (n), mean, standard deviation (SD), median, minimum, and maximum values. For PK parameters, the geometric mean and coefficient of variance (CV) will also be presented. All continuous summaries will display the minimum and maximum value with the same number of decimals collected in the data. The median, mean, geometric mean and CV will display 1 additional decimal, and the SD and SE will display 2 additional decimals. For categorical variables, frequencies and percentages will be reported. All percentages will be reported to 1 decimal; all p-values will be reported to 3 decimals.

All temperature measurements will be presented as degrees Celsius. Degrees in Fahrenheit will be converted with this formula:

$$T_C = (T_F - 32)*(5/9),$$

where T_C is a Celsius temperature and T_F is a Fahrenheit measurement.

All statistical comparisons will be performed using 2-sided tests at the 0.05 significance level, unless specifically stated otherwise. All null hypotheses will be defined as no treatment difference. All p-values are presented for informational purposes only; there will not be any adjustments for multiple comparisons.

All analyses, summary tables, figures, and data listings will be generated with SAS version 9.4 or higher. Specialized PK software will be used for some PK analyses.

Baseline is defined as the latest non-missing measurement taken prior to study drug administration.

All summaries will be by actual visit, no visit windows for analysis will be defined. In general, summaries will be by treatment groups, and will include a combined VIS410 treatment group, in addition to the individual low dose (2000 mg) VIS410, high dose (4000 mg) VIS410, and Placebo treatment groups, unless specified differently. Summaries of disposition, other baseline data, and adverse events will also include an overall column.

4.2 Missing Data Conventions

Partial and missing AE and concomitant medication dates will be imputed with maximum conservatism. If the onset date is missing or partial, the date will be compared as far as possible with the date of first dose of study medication. If no month is present and it is in the same year as the date of first treatment, or the year and month are the same as the first treatment date, the onset date will be imputed as the date of first treatment. Otherwise it will be imputed as 01 January in the available year, or the first day of the month and year available. End dates will be imputed as 31 December in the available year, or the last day of the available month and year collected. Partial dates will be presented in listings, along with classifications of TEAE for AEs or Prior/Concomitant/Both for medications.

Missing data will generally be left as missing, except for partial and missing AE and concomitant medication dates. Special cases, e.g. below the limit of quantification, will be described in the sections that describe the specific parameter's analysis.

5 STUDY SUBJECTS

5.1 Analysis Populations

5.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects randomized to treatment.

5.1.2 Modified Intent-to-Treat Population

The mITT population will include all subjects who receive IV study drug and are confirmed influenza A positive by a molecular test at the central virological laboratory.

5.1.3 Safety Population

The safety population will include all ITT subjects who received IV study drug. The safety population summaries will be based on the actual treatment received.

5.1.4 Pharmacokinetic Population

The PK population will include all subjects who receive IV study drug and have at least 1 PK parameter that can be calculated. Nasopharyngeal swabs that are collected outside of the protocol defined sampling time points for PK (i.e. when influenza-like symptoms are present) will not be used to determine PK parameters. Nasopharyngeal PK parameters will only be calculated for the first 50 subjects enrolled.

5.2 Protocol Deviations

Major protocol deviations are compliance issues that impact subject safety or the scientific integrity of the study data. All deviations will be evaluated and classified as major or minor by the study team before database lock and unblinding. Major and minor deviations will be summarized by treatment group with counts and percentages of subjects with at least 1 deviation. If a subject has both minor and major deviations, that subject will be counted as having a major deviation. All deviations will be listed.

5.3 Disposition of Subjects

The following subject data will be summarized for each treatment group and overall for the ITT and mITT populations:

- Overall number of subjects screened
- Number of subjects randomized
- Number of subjects randomized but not treated
- Number and percentage of subjects in each analysis population
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who prematurely discontinued the study as well as number and percentage of subjects for each reason for discontinuation.

Percentages will be calculated using the ITT or mITT population as a denominator. All disposition data will be listed.

An additional summary of subjects enrolled by region and site for each treatment group and overall will be presented. A listing of subject enrollment and disposition information will be provided for all subjects. An additional listing of subjects who prematurely discontinued the study will also be presented. Inclusion of subjects into each of the analysis populations (ITT, Safety, mITT, and PK) will also be listed.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1 Demographics and Baseline characteristics

Descriptive statistics of the general demographic and Baseline characteristics for each treatment group and overall will be presented. Baseline variables age (years), height (cm), weight (kg), body mass index (BMI, kg/m^2), both baseline HAI titers (H1 and H3), and time since onset of influenza symptoms will be summarized with n, mean, SD, median, minimum and maximum; time to onset of influenza will also be dichotomized (< 48 hours or ≥ 48 hours) and summarized with counts and percentages. Counts and percentages will be presented for each category of gender, race, ethnicity, vaccination status, confirmed influenza A by method of diagnosis (RAT, PCR, $TCID_{50}$), and influenza subtype.

The demographic and Baseline data will be summarized in the ITT and mITT populations. All demography and Baseline data will be listed.

The following definitions and conversions will be used:

- Height (in) *2.54 = height (cm)
- Weight (lb) /2.2 = weight (kg)
- BMI = weight (kg)/ $height^2$ (m^2)
- Time since onset of influenza (hours) = date/time of infusion start – date/time of onset of symptoms. If onset time is missing, it will be imputed as 00:00 on the 24-hour clock.

6.2 Medical history

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 and summarized by System Organ Class (SOC), Preferred Term (PT), and treatment with counts and percentages in the ITT and mITT populations. A subject will only be counted once in an SOC and an SOC/PT combination. All medical history data will be listed.

6.3 Prior medications

Prior medications are defined as medications that start on or before the date of study drug IV infusion and/or are declared as "Pre-study" on the medications eCRF page. Protocol-specified pre-treatment medications will be summarized as prior medications. Prior Medications will be coded with the World Health Organization Drug (WHODrug) Dictionary, Sep 2016 and summarized by Anatomical Therapeutic Chemical (ATC) Level 4, PT, and treatment in the ITT and mITT populations. A subject will only be counted once in an ATC class and an ATC class/PT combination. All eCRF medication data will be listed, including the WHO Drug ATC class, PT and the investigators verbatim description of the medication.

7 CONCOMITANT MEDICATION

Concomitant medications are defined medications that are being taken while on study drug. Any prior medication that cannot be confirmed as stopping before the start of study drug IV infusion will be classified as both a prior and a concomitant medication. Concomitant medications will be coded with the WHODrug, Sep 2016 dictionary, and summarized by ATC Level 4, PT, and treatment in the safety population. A subject will only be counted once in an ATC class and an ATC class/PT combination. Medications that are ongoing on the date of study drug IV infusion will be summarized as both prior and concomitant. All eCRF medication data will be listed, including the WHO Drug ATC class, PT term, the investigators verbatim description and classification as Prior, Concomitant or Both.

A separate listing of concomitant antiviral medications taken for influenza through study day 100 will also be presented. Antiviral medications will be defined as those medications that exclude a subject from the sensitivity analysis of the overall FluPRO and viral shedding analyses.

8 TREATMENT EXPOSURE AND COMPLIANCE

The duration of infusion in minutes and volume of infusion will be summarized by treatment group with n, mean, SD, median, minimum and maximum in the Safety and mITT populations. The number and percentage of subjects in each treatment group who received diphenhydramine per protocol, received an NSAID per protocol, had an infusion interruption of > 15 minutes, and did not receive the full infusion will also be summarized in the Safety and mITT populations. If there are a large number of interruptions (10% or more), incomplete infusions, or subjects not receiving the protocol-specified pre-treatment medications, the duration of infusion and volume of infusion summaries may be repeated with subsets based on these dosing parameters. The decision to generate any subset summaries will be made before unblinding the study.

9 EFFICACY ANALYSES

The primary objective of this study is the safety and tolerability of a single IV dose of VIS410. Safety analyses are described in Section 13.

9.1 Main Efficacy Analysis

9.1.1 Patient Diary - Influenza Patient Reported Outcomes (FluPRO)

The FluPRO is a 32 question instrument that assesses occurrence and severity of influenza symptoms over the last 24 hours. The instrument questions, and the conversion from text to numeric values, are presented in Sec. 17.3.

The FluPRO data is collected at Day 1: Baseline, then every day through Day 10. These data will be summarized at each visit with counts and percentages by treatment group, including a combined low-dose and high-dose VIS410 group. This analysis will be performed using the mITT population.

The domain, component, and total symptom scores for an individual will be calculated as the mean of the questions that are non-missing. The minimum data requirement for calculating each of the domain symptom scores is: nose 3 of 4 items, throat 2 of 3 items, eyes 2 of 3 items, chest/respiratory 5 of 7 items, gastrointestinal 3 of 4 items, and body/systemic 8 of 11 items. Total symptom scores will only be calculated if the conditions of missing data for all domains are met.

The domain symptom scores are defined as:

- Nose: Running or dripping nose, congested or stuffy nose, sneezing, sinus pressure
- Throat: Scratchy or itchy throat, sore or painful throat, difficulty swallowing
- Eyes: Teary or watery eyes, sore or pain eyes, eyes sensitive to light
- Chest/Respiratory: Trouble breathing, chest congestion, chest tightness, dry or hacking cough, wet or loose cough, coughing, coughed up mucus or phlegm
- Gastrointestinal: Nausea, stomach ache, vomiting, diarrhea
- Body/Systemic: Felt dizzy, head congestion, headache, lack of appetite, sleeping more than usual, body aches or pains, weak or tired, chills or shivering, felt cold, felt hot, sweating

The component symptom scores are defined as:

- Upper Respiratory Tract: Runny or dripping nose, congested or stuffy nose, scratchy or itchy throat, sore or painful throat, sneezing, difficulty swallowing, teary or watery eyes, sore or painful eyes, eyes sensitive to light,
- Lower Respiratory Tract: Trouble breathing, chest congestion, chest tightness, coughing, dry or hacking cough, wet or loose cough, coughed up mucus or phlegm
- Generalized: Nausea, vomiting, diarrhea, stomach ache, felt dizzy, sinus pressure, head congestion, headache, lack of appetite, sleeping more than usual, body aches or pains, weak or tired, chills or shivering, felt cold, felt hot, sweating

Time to resolution (in days) for the total symptom score, each domain symptom score (nose, throat, eyes, chest/respiratory, gastrointestinal, body/systemic) and each component symptom score (upper respiratory tract, lower respiratory tract, and generalized) will be summarized using n, mean, SD, median, minimum, and maximum. Kaplan-Meier methods will also be used to calculate the median time, 25th percentile, and 75th percentile time to resolution. These summaries will be by treatment group and include the combined low-dose and high-dose VIS410 groups in the mITT population. For individual symptom questions 1 to 32, a value of 0 or 1 corresponds to resolution of that symptom. Time to resolution of the total symptom, domain symptom scores and component symptom scores will be defined as the maximum time to resolution for the individual questions that comprise that total, domain or component symptom score.

The duration of an individual symptom will be defined as the earliest visit day from 2 consecutive answers of 'no symptom' defined as 'Not at all' or 'A little bit' for questions 1 – 27; 'Never' or 'Rarely' for questions 28 - 30 and '0 times' or '1 time' for questions 31 and 32. The duration of total symptom score, domain symptom scores, or component symptom scores will be primarily defined as the earliest visit day from 2 consecutive means ≤1.0; and as an exploratory endpoint as the maximum value of duration across the individual symptoms questions that comprise that total, domain or component symptom score. A missing value cannot contribute to the 2 consecutive 'no symptom' days. If a subject has 'no symptoms' at Baseline for a question, total symptom score, domain symptom scores, and component symptom scores, duration will be defined as zero for that question. If a subject has not had 2 consecutive 'no symptom' responses or 2 consecutive means ≤1.0 by the Day 10 FluPRO survey, the subject's data will be listed as ">10" and summarized as 10 days. Kaplan-Meier methods will also be used to calculate the median time, 25th percentile, and 75th percentile time to resolution.

The total symptom score, the 6 domain symptom scores, and the 3 component symptom scores will be summarized by treatment group at each visit (including change from baseline and percent change from Baseline to each visit), including the combined low-dose and high-dose VIS410 group with n, mean, SD, median, minimum, and maximum by treatment group, including a combined low-dose and high-dose VIS410 group.

The count and percentage of subjects with a mean score ≤1.0 for the total symptom score, 6 domain symptom scores, and 3 component score will be summarized at each post-baseline visit. An additional summary of counts and percentages of subjects with a score of 0 or 1 for all of the individual symptom scores composing the total symptom score, 6 domain symptom scores, and 3 component symptom scores will also be presented for each post-baseline visit. These summaries will also be presented by region: USA, South Africa, and the rest of the world.

Area under the curve (AUC) for the total symptom score, 6 domain symptom scores, and 3 component symptom scores will be calculated using the linear trapezoidal rule, i.e. $AUCt_{i,}$-$t_i+1=1/2*(S_i + S_i+1)*(t_i+1 – t_i)$ where S_i is the total symptom score at time point t_i. All time points from pre-dose to Day 10 will be considered.

A sensitivity analysis of the total symptom score, domain symptom scores, and component symptom scores will be conducted by repeating the above analysis in the mITT population,

excluding subjects who received antiviral therapy for influenza during the first 10 days of the study. Determination of applicable antiviral therapy for influenza will be defined before the study is unblinded.

Additional exploratory analysis, including but not limited to evaluation of sums instead of means of symptom scores, may be performed for the total symptom score, 6 domain symptom scores, and 3 component symptom scores.

9.1.2 Patient Diary – Oral Temperature

Subjects are instructed to record an oral temperature every morning and evening, starting on Day 1 and continuing through Day 10. This data will be summarized, in degrees Celsius, at each visit/time point with continuous statistics n, mean, SD, median, minimum, and maximum. These summaries will be presented by treatment group, including the combined low-dose and high-dose VIS410 group. This summary will be performed using the mITT population. Time to recovery to normal temperature will be assessed for each treatment arm and the combined low-dose and high-dose VIS410 group. Normal temperature will be defined as 2 consecutive oral temperature of <37.2°C (99°F). Kaplan-Meier methods will be used to calculate the median time, 25th percentile, and 75th percentile time to normal temperature. This analysis will only include mITT subjects with a baseline temperature of >38°C.

9.1.3 Complications of Influenza

The number and percentage of subjects in the mITT population with at least 1 complication of influenza will be summarized with counts, percentages, and the exact 95% CI of subjects with complications. A similar summary will be presented for each of the main complications of influenza: pneumonia, myocarditis, worsening of chronic bronchitis, otitis, sinusitis, death, other chronic pulmonary diseases, and other complications. These summaries will be presented for each treatment group as well as the combined low-dose and high-dose VIS410 groups.

9.1.4 Hospitalizations

Hospitalization parameters will be summarized for each treatment group and the combined low-dose and high-dose VIS410 groups, and overall subjects in the mITT population. The number and percentage of subjects hospitalized, and hospitalized for influenza-related complications, will be summarized with counts and percentages. The duration of hospitalization in days will be summarized with n, mean, SD, median, minimum, and maximum in the mITT population.

9.1.5 Influenza A Relapse

The incidence of relapse/reinfection will be summarized with counts and percentages in the mITT population for all 3 treatment groups and the combined VIS410 low-dose and high-dose groups as well as overall.

The initial screening for possible relapse will be based on MedDRA coded AE preferred terms of Flu-like symptoms, Flu-like aching, Flu-like illness, or Influenza-like symptoms. The start date

for this AE must be during the 100-day follow-up period and ≥7 days after any earlier influenza AE to ensure this is a relapse, rather than a worsening of initial symptoms. Relapses must be confirmed with a positive virology test.

10 PHARMACOKINETIC ANALYSES

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) will be used to estimate PK parameters in serum and from nasopharyngeal secretions as 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 on both linear and logarithmic scales. Additional plots and PK parameters may be generated as appropriate.

The following PK parameters will be determined for VIS410 in serum (all subjects) and/or from nasopharyngeal secretions (only in the first 50 subjects enrolled):

- C_{max}: maximum observed concentration
- T_{max}: time of C_{max}
- T_{last}: time of the last measurable concentration
- $AUC_{0-\infty}$: area under the concentration-time curve from time 0 extrapolated to infinity
- $AUC_{\%extrap}$: percent extrapolated to $AUC_{0-\infty}$
- 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 in subjects with both values available

Additional PK parameters may be determined as appropriate.

A population PK analysis using mixed-effects modeling may be conducted to estimate the typical values and inter-patient variability of VIS410 PK parameters in serum and/or nasopharyngeal secretions and to assess the effect of covariates on model parameters. Data from this study may also be pooled with data from prior studies. If conducted, this analysis will be presented in a separate report outside the CSR.

10.1 Serum Pharmacokinetics

Serum concentrations and the computed PK parameters will be listed by treatment group and nominal time of collection. Summary statistics of serum concentrations and PK parameters will be presented by nominal time of collection including n, mean, geometric mean, standard deviation, CV, median, and ranges, as appropriate. Additional analyses and summaries may be generated as appropriate.

10.2 Nasopharyngeal Secretion Pharmacokinetics

Individual concentrations versus time profiles will be plotted on both linear and logarithmic scales in all subjects. Mean (± SD) or median concentrations versus time profiles will be plotted on both linear and logarithmic scales for the first 50 subjects enrolled that have the full PK profile collected. PK parameters listed above (Section 11) will be determined for VIS410 from nasopharyngeal secretions in the first 50 subjects enrolled only. Summary statistics of nasopharyngeal concentrations (first 50 subjects and in all subjects) and PK parameters (first 50 subjects only) will be presented by nominal time of collection including n, mean, geometric mean, standard deviation, CV, median and ranges, as appropriate. Additional analyses and summaries may be generated as appropriate.

Correlations between serum PK parameters and nasopharyngeal PK parameters will be presented. The 2 ratios of nasal AUC/serum AUC from the Day 3 visit until the last measurement and to infinity, will also be summarized with these statistics.

11 PHARMACODYNAMIC AND EXPLORATORY ANALYSES

11.1 Anti-influenza A Antibodies

Titer of anti-influenza A antibodies (H1 and H3 strains) will be summarized at Baseline/Day 1 and Day 28 with n, mean, SD, geometric mean, CV, minimum and maximum by visit and treatment group for the mITT population. Values below the limit of quantification (BLQ) will be listed as <BLQ and summarized as zero. Values that are <10 (LLOQ) will be assessed as 5 and values >10240 (ULOQ) will be assessed as 10240.

11.2 Nasopharyngeal Viral Load

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) will be used to calculate peak viral load (VL) and the area under the viral load-time curve (VL AUC). Viral load at each study visit, proportion of subjects with negative results at each study visit, peak VL, and VL AUC based on qRT-PCR and $TCID_{50}$ from nasopharyngeal secretions will be summarized with n, mean, SD, geometric mean, CV, minimum and maximum values in the mITT population overall and per influenza A virus subtype. All available viral data within the mITT population will be assessed to calculate proportion of subjects with negative results at each study visit. For all other calculated parameters, viral load will be assessed on all samples in the mITT population collected through the Day 7 visit. In addition, VL and VL AUC for the first 50 subjects will be listed through Day 14 (no summary statistics will be presented). For missing data on Day 3, Day 5 and Day 7, the analysis will be conducted without imputation and with the last observable measurement carried forward (LOCF). For missing data on Day 1, the analysis will be conducted by replacing the missing data with the Day 3 observable measurement. Subjects missing both Day 1 and Day 3 virology data will be removed from the analysis.

A t-test will be used to assess the difference between treatment groups in the VL AUC and peak VL from nasopharyngeal swabs based on qRT-PCR and $TCID_{50}$. If the assumptions needed for the t-test are not met, log transformation and/or non-parametric methods will be used.

Chi-square methods will be used to compare differences in treatment groups relative to placebo for the proportion of subjects with negative results on Day 3, Day 5 and Day 7 study visits.

A sensitivity analysis will also be performed; the data summary will be repeated in the mITT population excluding subjects who received antiviral therapy during the study. Determination of applicable antiviral therapy will be defined before the study is unblinded. All viral load data generated per the analytical plan will be listed.

For the influenza A virus subtype H3, virus load data measured by $TCID_{50}$ will be read out by both hemagglutination and NP-ELISA. The sensitivity is higher for NP-ELISA; therefore, all viral load parameters will be calculated using the data from NP-ELISA only.

11.2.1 Handling of values below a threshold

For the calculation of qRT-PCR parameters, any value which is not recorded as a number but expressed as a value below a detection limit will be imputed by half the value of the declared detection limit itself. For samples reported as qRT-PCR negative the value will be imputed to zero.

qRT-PCR examples:

- If the database contains values like "<2.18", half the value of the detection limit (1.09) will be used for calculating parameters.
- If the database contains values like "NEG", zero will be used for calculating parameters.

For the calculation of $TCID_{50}$ parameters, any value which is not recorded as a number but expressed as a value below a detection limit will be imputed to half the value of the declared detection limit for the first sample and the remainder values expressed as a value below a detection limit will be imputed to zero. qPCR negative samples that are not tested for TCD50 will be imputed to zero.

$TCID_{50}$ example:

- If the database contains values like "<0.75", the following rules will be used for calculating parameters
    - 0.375 will be used for the first value reported as "<0.75",
    - zero will be used for all remaining values reported as "<0.75"

11.3 Time to Resolution of Viral Load

Median time to cessation of viral shedding, determined by qRT-PCR and $TCID_{50}$ results, and the 95% CI about the median, will be presented for each treatment group. This analysis will use Kaplan-Meier methods. Additional exploratory statistical analyses may be conducted as appropriate. Time to resolution of viral load will be assessed on all samples in the mITT population collected through the Day 7 visit. For missing data on Day 3, Day 5, and Day 7, the analysis will be conducted without imputation and with the last observable measurement carried forward (LOCF). For missing data on Day 1, the analysis will be conducted by replacing the missing data with the Day 3 observable measurement. Subjects missing both Day 1 and Day 3

virology data will be removed from the analysis. Resolution of viral load is considered to be one BLQ or lower measurement with no samples following that which are greater than the BLQ.

The following virology parameters will be derived:

- Time to resolution of viral shedding from end of infusion
    - Number of days from end of infusion until virus is no longer detectable (at or below the limit of detection) with no samples following that are greater than the BLQ through Day 7 visit
    - If virus is still above level of detection at the end of the study, the last day of viral collection through Day 7 visit will be used
- Time to resolution of viral shedding from onset of symptoms
    - Number of days from onset of symptoms until virus is no longer detectable (at or below the limit of detection) with no samples following that are greater than the BLQ through Day 7 visit
    - If virus is still above level of detection at the end of the study, the last day of viral collection through Day 7 visit will be used

11.4 Resistance Analysis

Genotypic and phenotypic assessment will be conducted to determine the emergence of VIS410-resistant viruses. Sample selection for genotypic testing will be based on primary virology qPCR data. Phenotypic analysis will be performed based on the genotypic analysis. Results will be summarized in a genotypic report and a phenotypic report.

11.5 Exploratory Pharmacokinetic/Pharmacodynamic Analyses

Associations between serum VIS410 PK exposure parameters (AUC, Cmax) with virology endpoints will be evaluated. The dependent variables (endpoints) which will be explored in this analysis will be:

- Viral Load AUC ($TCID_{50}$ and qRT-PCR)
- Peak Viral Load ($TCID_{50}$, qRT-PCR)
- Duration of viral shedding ($TCID_{50}$, qRT-PCR)

The independent variables (PK exposure parameters) will include serum VIS410 AUC and Cmax. Univariable analyses will be conducted to explore the relationship between independent variables and dependent, as summarized above. Various techniques will be used to explore exposure-response relationships. 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, as appropriate. Decisions with regards to methods used will be based on the nature of the data, and strengths of relationships identified via graphical evaluation. If appropriate, continuous independent variables will be evaluated as such, and also as categorical variables (grouping subjects into exposure categories). Categories based on subject groupings will include quartiles, but also the implementation of

Classification and Regression Tree Analysis (CART) to identify significant target breakpoints. Results of the exploratory analyses may be reported in the clinical study report, or may be reported separately.

11.6 Anti-drug Antibodies

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

12 SAFETY ANALYSES

All safety analysis will be carried out using the safety population and the subject's actual treatment received.

12.1 Adverse Events

A TEAE is defined as an adverse event that starts on or after the date of study drug IV infusion. AEs that start on the day of infusion will be classified as TEAEs if the "Same day as infusion" question is answered as "Started after the infusion." All AEs will be coded using MedDRA version 19.1.

An overall summary of AEs and TEAEs will be presented by treatment group, including the combined low-dose and high-dose VIS410, and overall subjects, with subject counts, percentages, and the exact 95% CI for the percentage of subjects with the event. This summary will include subjects with any AE, any treatment-related AE, any TEAE, any treatment-related TEAE, any serious TEAE, any treatment-related serious TEAE, any TEAE of special interest (AESI), hypersensitivity reaction, anaphylactic reaction, any injection site AE, TEAEs by intensity, any moderate TEAE, any severe TEAE, TEAEs leading to study infusion discontinuation , treatment-related TEAEs leading to study infusion discontinuation, TEAEs leading to death, and treatment-related TEAEs leading to death.

TEAE definitions:

- All AESIs will be defined by the eCRF field event type - AESI
- Injection site AEs will be defined by the eCRF field event type - injection site AE
- Treatment related AEs will be defined by the investigators determination of the relationship as a reasonable possibility.
- Hypersensitivity and anaphylaxis reactions will be defined by clinical evaluation of TEAEs per the Safety Plan
- TEAEs leading to study infusion discontinuation will be defined by an answer of permanently discontinued as the eCRF action taken for an AE during infusion.

This summary will also be presented by region: US, Africa, Rest of the World.

A summary table by treatment group will present the number and percentage of subjects with TEAEs by SOC and SOC/PT. Subjects with multiple TEAEs within an SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. This table will also present a summary of subjects with any TEAE.

Similar summaries will be presented for Serious TEAEs, AESIs, injection site TEAEs, treatment-related TEAEs, TEAEs leading to study infusion discontinuation and TEAEs leading to death. The TEAE definitions for these tables will be the same as used in the overall summary of TEAEs.

A summary table by treatment group will be presented summarizing the intensity (mild, moderate, or severe) associated with each SOC and SOC/PT. A subject will be counted only once for an SOC or an SOC/PT combination. If a subject experiences multiple events in the same SOC or SOC/PT the highest recorded intensity will contribute counts to the summary table.

A summary table, by treatment group, will be presented for the TEAE relationship (reasonable possibility or no reasonable possibility) associated with each SOC and SOC/PT. A subject will be counted only once for an SOC or an SOC/PT combination. If a subject experiences multiple events in the same SOC or SOC/PT the closest relationship to study drug will contribute counts to the summary table.

12.2 Clinical Laboratory Tests

Hematology, blood chemistry, and urinalysis data are collected at Screening, Day 5, Day 14, and Follow-up/End of Treatment. They will be summarized by treatment group at each visit, as well as change from Baseline for continuous parameters at post-baseline visits.

- Hematology: hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) with differential, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets, and their change from Baseline, will be summarized by treatment group at each visit with continuous statistics (n, mean, SD, median, minimum and maximum).

- Chemistry and Coagulation: albumin, alkaline phosphate, alanine amino transferase, aspartate amino transferase, bicarbonate, total bilirubin, direct bilirubin, blood urea nitrogen (or urea), calcium, chloride, creatinine, lactate dehydrogenase, phosphate, inorganic, potassium, total protein, sodium, partial thromboplastin time, and activated partial thromboplastin time, and their change from Baseline, will be summarized by treatment group at each visit with continuous statistics (n, mean, SD, median, minimum and maximum).
  - Glucose is only collected at Baseline, so there will not be any post-baseline or change from baseline summaries.
  - Creatine kinase-MB, creatinine kinase, and troponin are only collected in special cases; they will be listed, but not summarized.

- Urinalysis:
  - Specific gravity and pH, and their change from Baseline, will be summarized by treatment group at each visit with continuous statistics (n, mean, SD, median, minimum and maximum).
  - Categorical parameters glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase will be summarized with counts and percentages by treatment group at each visit.
  - Urine sedimentation count (erythrocytes [RBC], leukocytes [WBC], and epithelial cells) and urine microscopy (crystals, casts, and bacteria) will be listed.

Summaries of counts and percentages of laboratory parameters that are Low, Normal, and High compared to the reference ranges will be presented by treatment at each visit and time point. Shift tables will be presented for laboratory parameters with defined DMID grades. DMID grades are defined in Appendix 17.4, DMID Adult Toxicity Table.

All clinical laboratory results will also be listed; these listing will be sorted by subject, visit date, and lab parameter; they will also include DMID grades and the low, normal and high value flags.

Separate listings of subjects with any clinical laboratory test result outside the reference ranges will also be presented for hematology, chemistry and coagulation, and urinalysis parameters. For these listings, if a subject has a DMID grade 1 or higher value, or low and/or high flag for a parameter, or a non-normal value for a categorical urinalysis parameter, all data for that subject/parameter will be presented. These listings will be sorted by subject, parameter, then visit. An additional listing will be presented for subjects with more than a 2-grade shift in DMID grades in any lab parameter.

12.3 Vital Signs

Vital signs heart rate, respiratory rate, temperature, systolic blood pressure, and diastolic blood pressures are recorded at Screening, on Day 1: Baseline, Day 1: End of Infusion Day 1: $\geq$ 2 hours post end of infusion, Day 3, Day 5, Day 7, Day 14, Day 28, Day 56 and Day 100/Early termination.

Tables presenting vital signs will display summary statistics (n, mean, SD, median, minimum and maximum) for the observed data at each visit. The corresponding changes from Baseline at the post-baseline visits will also be presented. Temperature will be presented in degrees Celsius.

Summaries of counts and percentages of vital signs that are Not Done, Normal, Abnormal, and Abnormal - Clinically Significant will be presented by treatment at each visit and time point. Shift tables of changes from baseline will also be presented.

Summaries of counts and percentages for subjects meeting Potentially Clinically Significant (PCS) Post-Baseline Vital Sign Criteria by visit will be presented. The PCS criteria for vital signs can be referenced in Appendix 17.5. A listing of these subjects meeting PCS criteria will also be provided.

All vital signs data will be listed. Subjects also self-monitor their temperature daily. These data will be summarized with the diary data, an efficacy endpoint; see sec. 10.1.2.

12.4 ECG Data

ECGs are performed at Screening and at Day 1: End of Infusion. The heart rate, PR interval, QRS interval, QT interval, and corrected QT, using the Fridericia correction (QTcF) will be summarized; change from Baseline at the post-infusion measurement will also be summarized. The QTcF calculation will be derived within the EDC system.

Counts and percentages of subjects with QTcF interval prolongation categories of <450, >450 to ≤480, >480 to ≤500, and >500 msec, will be presented by treatment group and visit. A similar

summary will be presented for subjects with QTcF increases of <30, >30 to ≤60 and >60 msec from Baseline.

A summary of normal and abnormal results, as well as shifts from Baseline for the post-infusion ECG, will be summarized with counts and percentages by treatment group.

Any clinically significant ECG findings will be collected and summarized with AEs.

All ECG data will be listed. A listing of subjects with QTcF interval prolongation of >450 to ≤480, >480 to ≤500, and >500 msec and/or QTcF increases of >30 to ≤60 and >60 msec from Baseline will be presented.

12.5 Physical Exam

A complete physical exam is only performed at Screening. A targeted physical exam may be performed at the Investigator‘s discretion at any time point during the study. A summary of physical examination results at Baseline will be presented by treatment group. All physical exam data will be listed.

13 INTERIM ANALYSIS

Optional interim analyses may be performed after 75 subjects have completed the Day 28 visit and/or after all enrolled subjects have completed the Day 14 visit. If the interim analyses are performed, a list of needed TFLs will be provided to the independent unblinded biostatistics team. These TFLs may be presented as completely unblinded analyses or in a semi-unblinded fashion, i.e. using coded actual treatment groups.

A Data Safety Monitoring Board (DSMB) will be empaneled to monitor the safety of the enrolled subjects. The tasks and responsibilities of the DSMB will be documented in a separate document.

14 SOFTWARE AND PROGRAMMING SPECIFICATIONS

14.1 Statistical Software

All statistical analyses will be performed using SAS 9.4 or higher, in accordance with Pharm-Olam SOP 009-20- SAS Program Development and Change Control. Specialized PK software will be used for some PK analyses.

14.2 General Programming Specifications

All tables will include the sponsor name, protocol ID, “Page x of y” and “Draft” or “Final” in the header.

The last 2 footer lines will be:

1. Data Source: (a data set for listings, a listing reference for tables) left justified
2. “Program Location: E:\Projects\1016Visterra\Stats\Programs\xxx.sas” left justified and “Date-Time: DDMMMYYYY:HH:MM” right justified

15 REFERENCE LIST

International Conference on Harmonization. Statistical Principles for Clinical Trials (E9), 5 February 1998.

16 APPENDICIES

16.1 Changes to the Protocol Specified analyses

ADA data at Day 14 will not be analyzed.

Nasopharyngeal viral load samples will only be analyzed for qPCR and $TCID_{50}$ until Day 7, unless still positive on Day 7, and then samples will also be analyzed on Day 14. No PCR or $TCID_{50}$ samples are planned to be analyzed post-Day 14.

QTcF interval prolongation categories were updated to <450, >450 to ≤480, >480 to ≤500, and >500 msec and categories for QTcF increases were updated to <30, >30 to ≤60 and >60 msec from Baseline.

16.2 Table 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
Chemistry [12]	X							X		X			X
Hematology [12]	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]
Urinalysis [12]	X							X		X			X
Instructions conmeds and FluPRO	X												
Observation in unit				X	X	X							
FluPRO completion [13]		X					X—			—X			
FluPRO compliance						X	X	X	X				
FluPRO collection, review and reinstructions							X	X	X				
AESIs		X—									—X		X [14]
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 [15]			X										
VIS410/placebo infusion [16]				X									
Serum PK			X [17]		X [18]		X	X	X	X	X	X	X
Nasopharyngeal swab [19]			X [17]				X	X	X	X [20, 21]	X [20,21]	X [20,21]	X [20,21]
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] See Laboratory Assessments for list of tests in Appendix 1.

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

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

[15] 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.

[16] 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.

[17] Within 1 hour prior to VIS410 administration.

[18] Sample collected within 30 minutes after completing the infusion of VIS410/placebo.

[19] Nasopharyngeal swabs will be obtained from both nostrils (1 swab per nostril).

[20] Will be done for the first 50 subjects enrolled only.

[21] If a subject presents with or reports influenza-like illness, additional swabs (1 swab per nostril) should be taken (see Section 7.1.5).

16.3 FluPRO Questionnaire

The FluPRO questionnaire collects information on influenza symptoms over the last 24 hours. These questions have possible answers of Not at all, A little bit, Somewhat, Quite a bit, or Very much. 'Not at all' is considered 'no symptom'.

1. Runny or dripping nose
2. Congested or stuffy nose
3. Sinus pressure
4. Scratchy or itchy throat
5. Sore or painful throat
6. Difficulty swallowing
7. Teary or watery eyes
8. Sore or painful eyes
9. Eyes sensitive to light
10. Trouble breathing
11. Chest congestion
12. Chest tightness
13. Dry or hacking cough
14. Wet or loose cough
15. Felt nauseous
16. Stomach ache
17. Felt dizzy
18. Head congestion
19. Headache
20. Lack of appetite
21. Sleeping more than usual
22. Body aches or pains
23. Weak or tired
24. Chills or shivering
25. Felt cold
26. Felt hot
27. Sweating

For numeric summaries, Not at all = 0; A little bit=1; Somewhat=2; Quite a bit=3; Very much=4.

These questions have possible answers of Never, Rarely, Sometimes, Often, Always. 'Never' is considered 'no symptom'.

28. Sneezing
29. Coughing
30. Coughed up mucus or phlegm

For numeric summaries, Never = 0; Rarely = 1; Sometimes =2; Often = 3; Always = 4'.

These questions have possible answers of 0 times, 1 time, 2 times, 3 times, 4 or more times. '0 times' is considered 'no symptom'.

31. How many times did you vomit?
32. How many times did you have diarrhea?

For numeric summaries 0 times = 0; 1 time = 1; 2 times = 2; 3 times = 3; 4 or more times = 4.

16.4 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

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 ----------	
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
Hypernatremia	146-150 mEq/ L	151-157 mEq/ L	158-165 mEq/ L	> 165 mEq/ L
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
Hyperkalemia	5.6 - 6.0 mEq/ L	6.1 - 6.5 mEq/ L	6.6 - 7.0 mEq/L	> 7.0 mEq/ L
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL
Hyperglycemia	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL
Hypocalcemia	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL
Hypercalcemia	10.6 - 11.5 mg/dL	11.6-12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL
Hypomagnesemia	1.4 - 1.2 mEq/ L	1.1 - 0.9 mEq/ L	0.8 - 0.6 mEq/ L	< 0.6 mEq/ L
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
Hyperbilirubinemia	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia	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

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

16.5 Potentially Clinically Significant (PCS) Post-Baseline Vital Sign Criteria

Parameter	Criteria
Heart Rate	>=120 bpm and increase of >=15 bpm from Baseline <=50 bpm and decrease of>=15 bpm from Baseline
Systolic BP	>=180 mmHg and increase of >=20 mmHg from Baseline <=90 mmHg and decrease of >=20 mmHg from Baseline
Diastolic BP	>=105 mmHg and increase of >=15 mmHg from Baseline <=50 mmHg and decrease of>=15 mmHg from Baseline

16.6 List of Proposed Tables, Figures, and Listings

16.6.1 Tables

Table	Title	Population
14.1.1.1	Subject Disposition	ITT
14.1.1.2	Subject Disposition	mITT
14.1.1.3	Subject Disposition by Country and Site	ITT
14.1.2.1	Summary of Protocol Deviations	ITT
14.1.3.1	Demographics and Baseline Characteristics	ITT
14.1.3.2	Demographics and Baseline Characteristics	mITT
14.1.4.1	Medical History	ITT
14.1.4.2	Medical History	mITT
14.1.5.1	Prior Medications	ITT
14.1.5.2	Prior Medications	mITT
14.1.6.1	Concomitant Medications	Safety
14.1.6.2	Treatment Exposure and Compliance	Safety
14.1.6.3	Treatment Exposure and Compliance	mITT
14.2.1.1A	Summary of FluPRO Domain Symptom Scores, Component Symptom Scores and Total Symptom Score by Means; Percent and Absolute Change from Baseline	mITT
14.2.1.1B	Summary of FluPRO Individual Questions, Domain Scores, Component Scores, and Total Symptom Score by Sum; Percent and Absolute Change from Baseline	mITT
14.2.1.2A	Kaplan-Meier Estimates of FluPRO Time to Symptom Resolution for Domain Scores, Component Scores and Total Score by Mean $\leq$1.0	mITT
14.2.1.2B	Kaplan-Meier Estimates of FluPRO Time to Symptom Resolution for Domain Scores, Component Scores, and Total Score by 0 or 1	mITT
14.2.1.3A	Summary of FluPRO Subjects with Domain Scores, Component Scores, and Total Score by Mean <1.0	
14.2.1.3B	Summary of FluPRO Subjects with Domain Scores, and Component Scores, and Total Score by 0 or 1	mITT
14.2.1.4A	Summary of FluPRO Subjects with Domain Scores, Component Scores, and Total Score by Mean $\leq$1.0 – By Region	mITT
14.2.1.4B	Summary of FluPRO Subjects with Domain Scores, Component Scores, and Total Score by 0 or 1 – By Region	mITT
14.2.1.5A	Summary of FluPRO Time-to-Symptom Resolution of Domain Scores, Component Scores and Total Score by Mean $\leq$1.0	mITT
14.2.1.5B	Summary of FluPRO Time-to-Symptom Resolution of Domain Scores, Component Scores and Total Score by 0 or 1	mITT
14.2.1.6A	Kaplan-Meier Estimates of Duration of Influenza Symptoms for Domain Scores, Component Scores, and Total Score by Mean $\leq$1.0	mITT

Table	Title	Population
14.2.1.6B	Kaplan-Meier Estimates of Duration of Influenza Symptoms for Domain Scores, Component Scores, and Total Score by 0 or 1	mITT
14.2.1.7A	Summary of FluPRO Area Under the Curve for Domain Scores, Component Scores, and Total Score by Mean	mITT
14.2.1.7B	Summary of FluPRO Area Under the Curve for Domain Scores, Component Scores, and Total Score by Sum	mITT
14.2.1.8A	Summary of FluPRO Area Under the Curve for Domain Scores, Component Scores, and Total Score by Mean- Excluding Subjects Who Received Antiviral Therapy in First 10 days of Study	mITT
14.2.1.8B	Summary of FluPRO Area Under the Curve for Domain Scores, Component Scores, and Total Score by Sum – Excluding Subjects Who Received Antiviral Therapy in First 10 days of Study	mITT
14.2.2.1	Summary of Oral Temperature Patient Diary Data	mITT
14.2.2.2	Kaplan-Meier Estimates of Median Time to Normal Temperatures	mITT
14.2.2.3	Influenza Symptom Complications	mITT
14.2.2.4	Summary of Hospitalizations	mITT
14.2.2.5	Summary of Influenza A Relapse	mITT
14.3.1.1	Overall Summary of Adverse Events	Safety
14.3.1.2	Overall Summary of Adverse Events by Region	Safety
14.3.1.3	Summary of Treatment Emergent Adverse Events	Safety
14.3.1.4	Summary of Treatment Emergent Adverse Events Occurring in >=5% of Subjects in Any Treatment Group	Safety
14.3.1.5	Summary of Serious Treatment Emergent Adverse Events	Safety
14.3.1.6	Summary of Treatment Emergent Adverse Events of Special Interest	Safety
14.3.1.7	Summary of Injection Site Adverse Events	Safety
14.3.1.8	Summary of Treatment-Related Treatment Emergent Adverse Events	Safety
14.3.1.9	Summary of Treatment Emergent Adverse Events Leading to Infusion Discontinuation	Safety
14.3.1.10	Summary of Treatment Emergent Adverse Events Leading to Death	Safety
14.3.1.11	Summary of Treatment Emergent Adverse Events by Relationship	Safety
14.3.1.12	Summary of Treatment Emergent Adverse Events by Intensity	Safety
14.3.5.1	Hematology - Summary and Change from Baseline	Safety
14.3.5.2	Hematology – Values Compared to Normal Range (Low, Normal, High)	Safety
14.3.5.3	Hematology – Shift Tables by Microbiology and Infectious Diseases (DMID) Grades	Safety
14.3.5.4	Chemistry and Coagulation - Summary and Change from	Safety

Table	Title	Population
	Baseline	
14.3.5.5	Chemistry and Coagulation – Values Compared to Normal Range (Low, Normal, High)	Safety
14.3.5.6	Chemistry and Coagulation – Shift Tables by Microbiology and Infectious Diseases (DMID) Grades	Safety
14.3.5.7	Urinalysis - Summary and Change from Baseline	Safety
14.3.5.8	Urinalysis – Categorical Parameter Summaries	Safety
14.3.5.9	Urinalysis – Shift Tables of Categorical Summaries	Safety
14.3.5.10	Vital Signs - Summary and Change from Baseline	Safety
14.3.5.11	Vital Signs – Summary of Not Done, Normal, Abnormal, and Clinically Significant	Safety
14.3.5.12	Vital Signs – Shift Tables of Not Done, Normal, Abnormal, and Clinically Significant	Safety
14.3.5.13	Summary of PCS Vital Sign Values	Safety
14.3.5.14	Electrocardiogram – Summary and Change from Baseline of QT Intervals	Safety
14.3.5.15	Electrocardiogram - Summary of Normal and Abnormal Results	Safety
14.3.5.16	Electrocardiogram – Shift Table of Normal and Abnormal Results	Safety
14.3.5.17	Electrocardiogram – Categorical Summary of QTcF Changes	Safety
14.4.1.1	Summary of Serum VIS410 Concentrations	PK
14.4.1.2	Summary of Serum VIS410 Pharmacokinetic Parameters	PK
14.4.1.3	Summary of Nasopharyngeal VIS410 Concentrations	PK
14.4.1.4	Summary of Nasopharyngeal VIS410 Pharmacokinetic Parameters	PK
14.4.2.1	Summary of Anti-influenza A Antibodies	mITT
14.4.2.2	Area Under the Viral Load-Time Curve (VL AUC) and Peak Viral Load (VL) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 7 <Viral Load Parameters Determined by qRT-PCR>	mITT
14.4.2.3	Area Under the Viral Load-Time Curve (VL AUC) and Peak Viral Load (VL) Based on $TCID_{50}$ from Nasopharyngeal Swabs Through Day 7 <Viral Load Parameters Determined by $TCID_{50}$>	mITT
14.4.2.4	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by qRT-PCR Through Day 7	mITT
14.4.2.5	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by $TCID_{50}$ Through Day 7	mITT
14.4.2.6	Percent of Subjects Negative for Viral Titer by Study Day Determined by qRT-PCR	mITT
14.4.2.7	Percent of Subjects Negative for Viral Titer by Study Day Determined by $TCID_{50}$	mITT
14.4.2.8	Summary of Anti-VIS410 Antibody Titer	mITT

16.6.2 Listings

Listing	Title	Population
16.2.1.1	Subject Enrollment and Disposition Information	All Subjects
16.2.1.2	Listing of Subjects Who Terminated Early from the Study	All Subjects
16.2.1.3	Subject Inclusion and Exclusion Criteria Deviations	All Subjects
16.2.1.4	Analysis Populations	All Subjects
16.2.2	Protocol Deviations	All Subjects
16.2.3	Subjects Excluded from the mITT Population	Subjects Excluded from mITT
16.2.4.1	Demographics	ITT
16.2.4.2	Medical History	ITT
16.2.4.3	Prior Medications	ITT
16.2.4.4	Concomitant Medications	ITT
16.2.5.1	Pretreatment Medications	ITT
16.2.5.2	Study Medication Administration and Accountability	Safety
16.2.6.1.1	FluPRO Questionnaire and Compliance for Individual Questions and Total Symptom Scores by Mean and Sum	mITT
16.2.6.1.2	FluPRO Questionnaire Domain Symptom Questions and Symptom Scores by Mean and Sum	mITT
16.2.6.1.3	FluPRO Questionnaire Composite Symptom Questions and Symptom Scores by Mean and Sum	mITT
16.2.6.1.4	FluPRO Questionnaire Compliance Information	mITT
16.2.6.2	Patient Temperature Log	mITT
16.2.6.3	Influenza Complications and Relapse	mITT
16.2.6.4	Hospitalizations	mITT
16.2.7	Adverse Events	Safety
16.2.8.1	Hematology Laboratory	Safety
16.2.8.2	Chemistry Laboratory	Safety
16.2.8.3	Urinalysis Laboratory	Safety
16.2.8.3.1	Clinical Laboratory Test Results Outside the Reference Ranges	Safety
16.2.8.3.2	Subjects with >2 category shift in DMID grades	Safety
16.2.8.4.1	Vital Signs	Safety
16.2.8.4.2	Subjects who met PCS Vital Sign Criteria	Safety
16.2.8.5.1	Electrocardiogram Data	Safety
16.2.8.5.2	Subjects with QTcF Changes	Safety
16.2.8.6	Physical Exam Data	Safety
16.2.8.7	Individual Listing and Summary of Virus Type by Subject	All Subjects
16.2.8.8	Individual Listing and Summary of Serum VIS410 Concentrations by Nominal Time Point	PK
16.2.8.9	Individual Listing and Summary of Serum VIS410 Pharmacokinetic Parameters	PK
16.2.8.10	Individual Listing and Summary of Nasopharyngeal VIS410 Concentrations by Nominal Time Point	PK
16.2.8.11	Individual Listing and Summary of Nasopharyngeal VIS410 Pharmacokinetic Parameters	PK
16.2.8.12	Individual Listing and Summary of qRT-PCR by Nominal Time	mITT

Listing	Title	Population
	Point	
16.2.8.13	Individual Subject Peak Viral Load (VL) and Area Under the Viral Load-Time Curve (VL AUC) Measured by qRT-PCR	mITT
16.2.8.14	Change from Baseline Viral Shedding [qRT-PCR] by Treatment Group	mITT
16.2.8.15	Individual Listing and Summary of $TCID_{50}$ by Nominal Time Point	mITT
16.2.8.16	Individual Subject Peak Viral Load and Viral Load AUC Measured by $TCID_{50}$	mITT
16.2.8.17	Change from Baseline Viral Shedding [$TCID_{50}$] by Treatment Group	mITT
16.2.8.18	Immunogenicity Data - ADA	PK
16.2.8.19	Immunogenicity Data - HAI	mITT

16.6.3 Figures

Figure	Title	Population
14.2.1	Kaplan-Meier Plot of Median Time to Normal Temperatures	mITT
14.2.2.1	Kaplan-Meier Plot of Median Time to Resolution of Domain Scores, Component Scores, and Total Score by Mean	mITT
14.2.2.2	Kaplan-Meier Plot of Median Time to Resolution of Domain Scores, Component Scores, and Total Score by 0 or 1	mITT
14.2.3.1	Kaplan-Meier Plot of Duration of Domain Scores, Component Scores, and Total Score by Mean	mITT
14.2.3.2	Kaplan-Meier Plot of Duration of Domain Scores, Component Scores, and Total Score by 0 or 1	mITT
14.4.1.1	qRT-PCR Median Viral Shedding versus Time Profiles	mITT
14.4.1.2	qRT-PCR Mean Viral Shedding versus Time Profiles	mITT
14.4.1.3	Individual Subject qRT-PCR Viral Shedding versus Time Profiles	mITT
14.4.1.4	$TCID_{50}$ Median Viral Shedding versus Time Profiles	
14.4.1.5	$TCID_{50}$ Mean Viral Shedding versus Time Profiles	mITT
14.4.1.6	Individual Subject $TCID_{50}$ Viral Shedding versus Time Profiles	mITT
14.4.1.7.1	Duration of Viral Shedding Measured by qRT-PCR from End of Infusion (Days)	mITT
14.4.1.7.2	Duration of Viral Shedding Measured by qRT-PCR from Onset of Symptoms (Days)	mITT
14.4.1.8.1	Duration of Viral Shedding Measured by $TCID_{50}$ from End of Infusion (Days)	mITT
14.4.1.8.2	Duration of Viral Shedding Measured by $TCID_{50}$ from Onset of Symptoms (Days)	mITT
14.4.2.1	Mean Serum VIS410 Concentration versus Time Profiles (linear and log-linear scales)	PK
14.4.2.2	Mean Serum VIS410 Concentration versus Time Profiles (linear and log-linear scales) by ADA status	PK
14.4.2.3	Individual Subject Serum VIS410 Concentration versus Time Profiles (linear and log-linear scales)	PK
14.4.3.1	Mean nasopharyngeal VIS410 Concentration versus Time Profiles (linear and log-linear scales)	PK
14.4.3.2	Mean nasopharyngeal VIS410 Concentration versus Time Profiles (linear and log-linear scales) by ADA status	PK
14.4.3.3	Individual Subject Nasopharyngeal VIS410 Concentration versus Time Profiles (linear and log-linear scales)	PK

16.7 Tables, Figures, and Listings Shells

Table shells are in a separate document. Shells will be completed after the SAP text is finalized.