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STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	Phase 2b, Multicenter, Randomized, Double-blind, Controlled Study to Evaluate the Efficacy and Safety of Intravenous VIS410 in Addition to Oseltamivir (Tamiflu®) Compared with Oseltamivir Alone in Hospitalized Adults with Influenza A Infection Requiring Oxygen Support
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Changes from Previous Version of SAP

SAP Version	Change from Previous Version	Reason	Revised SAP Sections
2.0	Population for Disposition Table 14.1.1.1 Changed from Enrolled to ITT	Change in analysis population	5.3, Appendix 16.6.1
	Details added regarding definition of baseline positivity based on viral load	Clarification of existing text	4.3, 9.2.10
	Addition of analysis based on mean VAS scores (summary table and figure) overall and in subsets based on time between symptom onset and treatment	Sponsor request	2.4.3, 3.3, 9.2.5
	Additional Subgroup added based on time between onset of symptoms and treatment	Subgroup for analysis of VAS scores	4.3
	Pairwise t-tests replaced by ANOVA based on ranks	Allows for contrast statements for all treatment comparisons utilizing all data	9.2.6
	Wilcoxon rank sum tests replaced by ANOVA based on ranks	Allows for contrast statements for all treatment comparisons utilizing all data	9.2.6
	Addition of summary analysis based on Sponsor-defined bacterial pneumonia	Complication of Influenza eCRF not correctly utilized	9.2.7
	Exact Mantel-Haenzel test and Cochran-Mantel-Haenzel test replaced by logistic regression	Allows for contrast statements for all treatment comparisons utilizing all data	9.2.1
	Additional details provided regarding the determination of anaphylaxis and hypersensitivity adverse events	Clarification of existing text	12.1

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANOVA	Analysis of Variance
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 SubjectReported 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}
VAS	Visual Analogue Scale
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 VIS410-203, a Phase 2b Multicenter, Randomized, Double-blind, Controlled Study to Evaluate the Efficacy and Safety of Intravenous VIS410 in Addition to Oseltamivir (Tamiflu®) Compared with Oseltamivir Alone in Hospitalized Adults with Influenza A Infection Requiring Oxygen Support.

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 pharmacokineticist will derive standard non-compartmental pharmacokinetics (PK) parameters. This analysis will be described within this SAP, see Section 10. Any other PK/PD analyses, including population PK modeling, are beyond the scope of this document.

This SAP is based on the protocol Version 3.0 dated 19 April 2018 and electronic Case Report Form (eCRF) version 4.0 dated 18 March 2018. 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 DESIGN AND OBJECTIVES

2.1 Trial Design

This is a Phase 2b, multicenter, randomized, double-blind, controlled study comparing the efficacy and safety of 2 dose levels of VIS410 (2000 and 4000 mg) in combination with oseltamivir vs oseltamivir alone in hospitalized subjects with influenza A infection requiring oxygen support. Subjects will be randomly assigned at a ratio of 1:1:1 using a permuted block randomization method to receive VIS410 at a dose of 2000 mg (low dose) or 4000 mg (high dose) or placebo (0.9% sodium chloride), administered as a single IV infusion over 2 hours. Randomization will be stratified by presence or absence of positive pressure ventilation (PPV) at baseline to ensure an even distribution across treatment arms. All subjects will receive oseltamivir 75 mg twice daily (BID) for 5 days (total of 10 doses) as part of standard of care. Treatment with oseltamivir may be extended for up to 5 additional days (up to 20 doses of total therapy) if clinical symptoms warrant further treatment as assessed by the Investigator. Depending on standard of care, subjects may have started oseltamivir therapy prior to randomization. All subjects will also receive a pretreatment regimen of diphenhydramine 50 mg PO or IV plus either ibuprofen 400 mg PO or acetylsalicylic acid 320-325 mg PO approximately 60 minutes before infusion. Approximately 120 evaluable subjects (40/arm) with confirmed influenza A infection will be treated.

Study assessments are outlined in the Schedule of Assessments (copy in Appendix 16.2). Subjects discharged from the hospital prior to Day 14 will attend the applicable out subject follow-up visit(s) (e.g., Day 3, Day 5, Day 7, Day 14) per Table 1. The total study duration for each subject (screening through study exit) will be approximately 8 weeks (Day 56).

2.2 Primary Hypothesis

The primary hypothesis for the study is that treatment with VIS410 + oseltamivir will lead to better clinical outcomes compared to oseltamivir alone.

The study is exploratory in nature and is not powered to demonstrate significant differences between treatment groups in primary or secondary outcome measures. The protocol intent is to collect sufficient information to identify the most appropriate candidate endpoints for subsequent Phase 3 study evaluation from among the primary and secondary endpoints described below. Statistical significance testing will therefore be used to assess the relative strength of evidence of the primary and secondary endpoints, to provide reasonable assurance that the endpoints chosen for a confirmatory Phase 3 trial will elucidate treatment differences between VIS410 plus oseltamivir versus oseltamivir alone.

2.3 Study Sample Size

Approximately 120 evaluable subjects will be enrolled. Subjects enrolled but not dosed are not considered evaluable. Ideally, the MITT population will be comprised of 120 subjects, but this is subject to enrollment efficiency and is not a stated requirement of the trial.

2.4 Study Objectives

The primary and secondary efficacy objectives are designed to determine the potential clinical benefit from virologic and clinical symptomology perspective of VIS410 when administered in combination with oseltamivir in this subject population. Additionally, the impact of the two VIS410 doses (2000mg and 4000mg, respectively) will be compared to evaluate for dose response. If both doses appear to be equivalent in efficacy, a comparison of pooled VIS410-treated subject data may provide greater statistical insight into the drugs behavior. Dose selection for future study based on outcomes from this trial will be influenced both by the efficacy and the side effect/safety profile of each of the tested doses.

2.4.1 Primary Objectives

Primary Efficacy Objective

- Evaluation of the effect of 2 dose levels of VIS410 + oseltamivir on clinical outcome as assessed by comparison of clinical status ordinal scale Day 7 scores between treatment groups, and between all VIS410 recipients versus placebo.
    - The ordinal scale is described in detail in Section 9.1
    - Four comparisons may be undertaken; 4000mg vs placebo, 2000mg vs placebo, pooled 4000mg+2000mg vs placebo and 4000mg vs 2000mg.

Primary Safety Objective

- Safety and tolerability of 2 dose levels of a single intravenous (IV) dose of VIS410 when administered in combination with oseltamivir in hospitalized subjects with influenza A infection

2.4.2 Secondary Objectives

Each of the following objectives will be assessed in the following pairings; 4000mg vs placebo, 2000mg vs placebo, pooled 4000mg+2000mg vs placebo and 4000mg vs 2000mg

- Among subjects requiring supplemental oxygen therapy at the time of enrollment with baseline room air oxygen saturation of ≤ 92%, time to cessation of oxygen (O2) support resulting in stable oxygen saturation (SpO2) by pulse oximetry. Stable SpO2 is defined as two consecutive SpO2 values of > 92% on room air that are at least 8 hours apart.
- For any subject requiring supplemental oxygen therapy at the time of enrollment (regardless of oxygen saturation), time to cessation of oxygen support.
- Evaluate the effect of 2 dose levels of VIS410 + oseltamivir vs oseltamivir alone on the following parameters, also examine these outcomes in pooled VIS410 + oseltamivir arms vs oseltamivir alone:

    - Assess Viral load parameters in upper respiratory samples (MITT population and subsets)
    - Time to clinical response
    - Time to cessation of ventilator support
    - Time to resumption of normal activities
    - All-cause and attributable Day 14, Day 28, and Day 56 mortality rates
    - Clinical status ordinal scale mean area under the curve for Days 1-7 and Days 1-14 using linear numeric scores for the ordinal categories.
    - Comparison of clinical status ordinal scale scores
    - Comparison of clinical status ordinal scale scores using modified ordinal scale criteria (i.e,. pooling of selected severity criteria scores)
    - Comparison of discrete ordinal scale parameters, including days of ventilator support, days in intensive care, and duration of hospitalization
    - Healthcare resource utilization
    - Analysis of time to alleviation of clinical signs and symptoms of influenza in the subset of subjects able to complete the Influenza Subject Reported Outcomes (FluPRO) Questionnaire at baseline and post-dose by Kaplan Meier analysis
    - Comparison of mean overall FluPRO scores by day and treatment arm, and mean FluPro Domain scores by day and treatment arm.
    - Proportion of subjects with newly documented bacterial pneumonia/superinfection
    - Proportion of subjects with influenza-related complications
- Pharmacokinetics of VIS410 in serum
- Immunogenicity of VIS410
- Emergence of resistance to VIS410 and oseltamivir

2.4.3 Exploratory Objectives

- Evaluate the effect of 2 dose levels of VIS410 + oseltamivir vs oseltamivir alone on Visual Analogue Scale (VAS) scores
- Evaluate the pharmacokinetics of VIS410 from nasopharyngeal secretions and tracheal aspirate (intubated subjects only)
- Assess the effects of VIS410 on viral load in tracheal aspirate (intubated subjects only)
- Assess correlations between virology, safety, VIS410 dose, pharmacokinetics, viral shedding, immunology, signs and symptoms of influenza, and other endpoints
- Assess the anti-influenza immune response

3 STUDY ENDPOINTS

3.1 Primary Endpoints

3.1.1 Primary Efficacy Endpoint

The primary efficacy outcome analysis compares Day 7 clinical status ordinal scale scores between treatment groups, and between all VIS410 recipients versus placebo. Clinical status is measured daily for 14 days using the below seven-level ordinal scale, with the classifications presented from the worst clinical outcome (death, score 7) to the best clinical outcome (discharged with full resumption of normal activities, score 1) in descending order; for each day, subject status will be classified by the worst clinical outcome (highest ordinal score) for which they qualify. For subjects who die prior to Day 7, the score of 7 will be carried forward through Day 14.

- Death
- ICU stay with mechanical ventilation
- ICU stay without mechanical ventilation
- Non-ICU hospitalization with supplemental oxygen
- Non-ICU hospitalization without supplemental oxygen
- Discharge with partial resumption of normal activities
- Discharge with full resumption of normal activities

3.1.2 Primary Safety Endpoint

- The proportion of subjects with AEs and SAEs following administration of VIS410

3.2 Secondary Endpoints

- Among subjects requiring supplemental oxygen therapy at the time of enrollment with baseline room air oxygen saturation of ≤ 92%, time to cessation of oxygen (O2) support resulting in stable oxygen saturation (SpO2) by pulse oximetry. Stable SpO2 is defined as two consecutive SpO2 values of > 92% on room air that are at least 8 hours apart.
- For any subject requiring supplemental oxygen therapy at the time of enrollment (regardless of oxygen saturation), time to cessation of oxygen support.
- The difference between VIS410 + oseltamivir and oseltamivir alone treatment groups in the following endpoints:
    - Assess viral load parameters in respiratory samples (MITT population, and subsets), specifically:
        - Peak virus concentration by qRT-PCR
        - Viral nasopharyngeal qRT-PCR AUC, BL to Day 5 and BL to Day 7
            - Include baseline-adjusted and non-adjusted comparisons.
        - Viral shedding by qRT-PCR versus time
            - Include baseline-adjusted and non-adjusted comparison.
        - Percentage of subjects in whom peak qRT-PCR value occurred post-baseline
        - Viral nasopharyngeal qRT-PCR AUC, BL to Day 7 and BL to Day 14
        - Peak virus concentration by $TCID_{50}$

- Percentage of subjects in whom peak $TCID_{50}$ value occurred post-baseline
- Viral nasopharyngeal $TCID_{50}$ AUC, BL to Day 5 and BL to Day 7
  - For $TCID_{50}$ AUC analyses, perform in both the MITT population and the MITT population subset comprised of subjects with positive BL nasopharyngeal viral cultures
  - Include baseline-adjusted and non-adjusted comparisons.
- Viral shedding by $TCID_{50}$ versus time
  - Include baseline-adjusted and non-adjusted comparison.
- Percentage of subjects with negative viral cultures by nominal study day (Day 3, Day 5, Day 7)
  - Perform this analysis in both the MITT population, and the MITT population subset comprised of subjects with positive BL nasopharyngeal viral cultures
- Kaplan Meier analysis of time to negativization of viral cultures, by treatment arm
  - Perform this analysis in both the MITT population, and the MITT population subset comprised of subjects with positive BL nasopharyngeal viral cultures
- Additional subset analyses will examine the above outcomes by:
  - Virus strain family, H1N1 versus H3N2
  - Duration of symptoms prior to treatment (< 72 hours, ≥ 72 hours)
  - Geographic region of enrollment

- Time to clinical response defined as resolution of at least 4 of 5 vital signs
  - Afebrile with core temperature ≤ 37.8°C, without use of antipyretics (oral ≤ 37.2°C)
  - Oxygen saturation ≥ 95% on room air without support or a return to pre-infection status, if pre-infection status was < 95%
  - Pulse rate ≤ 100/min
  - Systolic blood pressure ≥ 90 mm/Hg, without vasopressor use
  - Respiratory rate ≤ 24 beats per minute
- Clinical status ordinal scale mean area under curve for Days 1-7 and Days 1-14, using linear numeric scores for the ordinal categories.
- Comparison of clinical status ordinal scale scores for selected individual days (ie, Days 3, 4, 5, and 6)
- Comparison of clinical status ordinal scale scores using modified ordinal scale criteria (ie, pooling of selected severity criteria scores)
- Comparison of discrete ordinal scale parameters, including days of ventilator support, days in intensive care, and duration of hospitalization
- Number of days to resumption of usual activities
- All-cause and attributable mortality rates at Day 14, 28 and 56
- Total number of days in hospital and/or intensive care unit (ICU) from admission to discharge and rate of rehospitalization due to influenza A relapse/complication
- The incidence, severity, and duration of signs and symptoms of influenza-like illness as assessed by the FluPRO Questionnaire (see Appendix 16.3.1)
- The percentage of subjects with new bacterial pneumonia/superinfection

  - The percentage of subjects with influenza-related complications
- VIS410 pharmacokinetic (PK) parameters in serum
- Titer of anti-VIS410 antibody positive samples
- Genotypic and/or phenotypic assessment to determine the emergence of VIS410 and oseltamivir-resistant viruses

3.3 Exploratory Endpoints

- Average VAS scores at each visit
- Pharmacokinetics of VIS410 from nasopharyngeal secretions
- VIS410 concentrations in tracheal aspirates
- The difference in viral load between VIS410 + oseltamivir and oseltamivir alone treatment groups in tracheal aspirates of subjects on mechanical ventilation
- Titer of anti-influenza A antibodies by hemagglutinin inhibition assay (HAI) in serum
- Correlations between serum and/or nasopharyngeal PK with viral load, clinical symptoms, presence of ADAs, safety, and additional endpoints

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 clinical study report (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.

Since this is a phase 2 study rigorous control over type 1 error will not be used; 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.

4.3 Subgroups

The following subgroups may be used to provide further information on the primary efficacy endpoint and other clinical and virologic endpoints:

- Use of positive pressure ventilation
- Use of endotracheal intubation
- Time from onset of symptoms to VIS410 therapy
- Number of oseltamivir doses prior to VIS410
- Age categorization (<65 years, ≥65 years)
- Presence of underlying chronic lung disease
- Presence of coincident pneumonitis (pneumonia) at baseline
- Influenza A subtype
- Enrollment geographic region: Tiered assessments: initially, dichotomous (Northern Hemisphere and Southern Hemisphere), then with each hemisphere broken into two groups: North America (Canada and US) and Europe (Belarus, Belgium, Bulgaria, Estonia, France, Georgia, Latvia, Russia, Serbia, Spain, Ukraine and Georgia); and Asia/Oceania (Australia, Malaysia, New Zealand, Singapore, and Thailand) and South Africa. Enrollment geographic region: (northern hemisphere vs southern hemisphere)
- MITT subset comprised of subjects with positive baseline viral cultures based on TCID50
- Baseline HAI titer category (to matched virus subtype) (≤40 or >40)
- Time between onset of symptoms of influenza and treatment (< 72 hours or ≥ 72 hours)

5 STUDY SUBJECTS

5.1 Analysis Populations

5.1.1 All Enrolled Subjects

All enrolled subjects will include all subjects with a non-missing informed consent date. All enrolled subjects will be used for subject data listings and disposition summaries.

5.1.2 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects randomized to treatment. Any ITT population summaries will be based on the treatment to which they were randomly assigned.
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5.1.3 Modified Intent-to-Treat Population

The modified ITT (MITT) population will include all subjects who receive IV study drug and are confirmed influenza A positive. The MITT population summaries will be based on the treatment to which they were randomly assigned. All efficacy analyses including the primary efficacy analyses are performed in the MITT population.

5.1.4 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.

5.1.5 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.

5.2 Protocol Deviations

Major protocol deviations are compliance issues that have an impact on 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:

- 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 population as a denominator. All disposition data will be listed.

An additional disposition summary will be presented for the MITT population along with a summary of enrollment by region and site for each treatment group and overall. Region will be

categorized as North America (Canada and US), South Africa, Asia and Oceania (Australia, Malaysia, New Zealand, Singapore, and Thailand), and Europe (Belarus, Belgium, Bulgaria, Estonia, France, Georgia, Latvia, Russia, Serbia, Spain, Ukraine and Georgia)).

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), 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 categorized (<24 hours, 24 to < 48 hours, 48 to <72 hours, 72 to <96 hours, or ≥ 96 hours) and summarized with counts and percentages. Individual baseline HAI antibody status will be to the infecting virus subtype for each individual, and will be dichotomized (antibody titer ≤ 1:40, antibody titer > 1:40). Counts and percentages will be presented for each category of gender, race, ethnicity, positive pressure ventilation status, smoking status, vaccination status, confirmed influenza A by method of diagnosis (RAT, PCR, $TCID_{50}$, FIA, ELISA), HAI titer and influenza subtype. Counts and percentages will also be presented for comorbidities defined based on specific MedDRA terms and BMI (see Addendum 1) and number of days of Oseltamivir use prior to Study Day 1.

The demographic and Baseline data will be summarized for 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 (kg/m^2) = 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 20.1 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 before the study drug IV infusion. Prior medications will be coded with the World Health Organization Drug (WHODrug) Dictionary, Sep 2017 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 MEDICATIONS

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 2017 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. Medications will be sorted by medication start date within subject.

8 TREATMENT EXPOSURE AND COMPLIANCE

The duration of infusion in minutes and volume of infusion in mL 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

Efficacy analyses (including the primary efficacy analyses) will be performed using the MITT population and based on the treatment to which they were randomly assigned.

9.1 Primary Efficacy Analysis – Day 7 Ordinal Scale Status

The ordinal scale outcomes will be measured daily from Day 1 (Baseline) through Day 14 using the seven-level hierarchical scale with the classifications presented in the table below. The clinical outcomes therein are ordered from the worst clinical outcome to the best clinical outcome in descending order. For each day, subjects will be classified by the worst clinical

outcome for which they qualify. The number and percentage of subjects in each treatment group with each classification will be summarized for each day from Day 1 through Day 14, inclusive. For subjects who die prior to Day 7, the score of 7 will be carried forward through Day 14. If a subject is missing an ordinal scale value but is bracketed by the same values on immediately preceding and subsequent days, the value of the missing day will be imputed to be the same as the immediately preceding and subsequent days. If a subject is missing baseline ordinal scale values from Day 1, baseline values will be set to the Day 2 score. If subjects are missing Day 1 and Day 2, the baseline value will not be imputed. No other data will be imputed.

Table 1
Hierarchical Seven-Level Ordinal Scale for Clinical Outcomes

Clinical Outcome	Score
Death	7
ICU stay with mechanical ventilation	6
ICU stay without mechanical ventilation	5
Non-ICU hospitalization with supplemental oxygen	4
Non-ICU hospitalization without supplemental oxygen	3
Discharge with partial resumption of normal activities	2
Discharge with full resumption of normal activities	1

For use in overall summary statistical presentations, the ordinal categories will be assigned decreasing integer scores, with death a score of 7 and discharge with full resumption of normal activities a score of 1. Frequencies of ordinal scores at each visit will be generated and evaluated by proportional odds ratio analysis, as implemented by logistic regression, including a test of the proportional odds assumption and generation of common odds ratios. For this analysis, the reference response category will be 1= Discharge with full resumption of normal activities with the remaining response categories in numeric sequence to worst (7=Death). Additional exploratory analyses may be conducted to obtain a more complete understanding of the relationship of treatment to the ordinal response.

If it is determined that the level of care provided for particular subjects was driven by factors other than subject disease severity and acuity, data from these subjects will be analyzed in sensitivity analyses. Sensitivity analyses will be generated for ordinal score frequencies, AUC (baseline to Day 7 and to Day 14), post-baseline ordinal scale worsening and days in ICU. These sensitivity analyses will utilize updated ordinal scale measures based on data provided by investigators for subjects who remained in the ICU for reasons other than disease severity (for example, lack of non-ICU beds available). This information will be captured in a spreadsheet that will be locked and signed prior to database lock.

If the conclusions from the primary analysis of the Seven-Level Ordinal Scale differ from those resulting from the above sensitivity analyses, additional exploratory analyses will be performed. These analyses include but are not limited to assessments of whether the analysis conclusions

differ only at certain sites or whether the differences in the results remain after adjusting for covariates related to site, disease severity or other factors potentially related to outcome.

9.2 Other Analyses

9.2.1 Secondary Endpoints Assessing Ordinal Scale Status

The area under the curve (AUC) over time for a given subject will be calculated (using the linear trapezoidal rule) as the sum of the maximum ordinal score for each day up through Day 7 and Day 14. An analysis of treatment group differences will be performed on these per-subject AUC values using analysis of variance, with treatment group and randomization strata as fixed factors. A sensitivity analysis will be performed that excludes the category of death on study, to determine if death as an outcome skews the results; death as an outcome will also be analyzed as an independent secondary endpoint using all available death information.

A secondary analysis of treatment group effect on the difference in proportions of subjects with the worst (death) versus the best outcome (discharge from hospital and resumption of normal activities) will also be performed. This analysis does not use scores for the ordinal outcome but does account for ordinality and is therefore not dependent on the relationship of score to severity of outcome. P-values will be based on logistic regression treatment comparisons of best vs. worst vs. other categories adjusting for randomization strata.

An exploratory analysis will be performed through an exact categorical analysis of treatment group differences in the ordinal scale results using the worst outcome across all assessments on a per-subject basis.

Additional ordinal scale outcome assessments will include comparison of total numbers of days up to and including Day 14 at more severe scale values (death, time on ventilator, time in ICU) and proportions of subjects with ordinal scale worsening post enrollment.

Using the modified ordinal scale described in Table 2, frequency analyses by visit, AUC analyses (up to Day 7 and up to Day 14) and best versus worst versus other analyses will also be generated.

Proportion outcomes will be analyzed by categorical data analysis methods, including logistic regression adjusted for strata. Additional exploratory subgroup analyses may also be performed, for example, based on various age categories or other subgroup variables. Time from onset of symptoms to study treatment and the number of doses of oseltamivir (Tamiflu) prior to VIS410 treatment for the current case of influenza may be included as covariates in the analyses.

Table 2
Modified Five-Level Ordinal Scale for Clinical Outcomes

Clinical Outcome	Score
Death	5
ICU stay with mechanical ventilation	4
ICU stay without mechanical ventilation	3
Non-ICU hospitalization	2

Discharge	1

9.2.2 Time to Cessation of O2 Support

Among subjects requiring supplemental oxygen therapy at the time of enrollment with baseline room air oxygen saturation of ≤92%, time to cessation of O2 support will be analyzed using a Cox proportional hazards model where cessation of O2 support is defined as the finding of stable SpO2 at two consecutive room air SpO2 values that are separated by at least 8 hours greater than 92%. In the event that a subject has only one room air SpO2 measurement but has been stable off oxygen (for instance as an outpatient), the second value may be a carry forward of the prior measurement. Time from onset of symptoms to VIS410 treatment and the number of doses of oseltamivir (Tamiflu) prior to VIS410 treatment for the current case of influenza will be included as covariates in the analysis. P-values (using the Wald statistic) for each VIS410 dose versus placebo, VIS410 total versus placebo and VIS410 4000 mg versus 2000 mg will be presented.

9.2.3 Time to Clinical Response

Time to clinical response (days) is defined as time to the finding of normality (as defined below) for 4 out of 5 vital signs that will be determined upon physical examination. Clinical response is defined as:

- Afebrile with core temperature ≤ 37.8°C, without use of antipyretics (oral ≤ 37.2°C)
- Respiratory rate ≤ 24 beats per minute
- Oxygen saturation ≥ 95% on room air without support or a return to pre-infection status, if pre-infection status was < 95%
- Pulse rate ≤ 100/min
- SBP ≥ 90 mm/Hg, without vasopressor use

For determination of time to clinical response, achievement of any of the criteria above will carry forward to missing data at subsequent visits. Subjects who do not experience clinical response will be censored at the last available vital sign visit date. Time to Clinical response will be analyzed using Kaplan-Meier techniques.

Pre-infection oxygen saturation data on room air status was not collected on the CRF. Therefore, prior to database lock, for any subject with persistent oxygen saturation on room air <95%, a query to the investigator will be sent to request historic oxygen saturation on room air data. If a baseline oxygen saturation on room air value collected during 6 months prior to enrollment is available, the information will be captured and recorded in a spreadsheet maintained by data management at POI. This spreadsheet will be reviewed, signed and locked prior to database lock. This information will be used to define pre-infection oxygen saturation on room air for the purposes of calculating time to clinical response. If there are no available medical record data and oxygen saturation remains below 95% on room air, the subject will be analyzed as not experiencing clinical response.

Note, the number of vital signs abnormalities (utilizing the above criteria) may range from 0 to 5 for subjects enrolled in the trial, although the expectation is that all subjects will have at least one abnormality. Therefore, this analysis will be conducted in two ways. First, the probability of time to clinical response (defined as the finding of at least 4 of 5 normal vital signs using the criteria above) will be calculated via Kaplan-Meier; under this analysis, some subjects will have met criteria for a clinical response at baseline. Time to clinical response will be calculated as Date of

Event – Date of Day 1. If the event was not achieved then the value will be censored and calculated as Date of the last available assessment – Date of Day 1. P-values for each VIS410 dose versus placebo, VIS401 total versus placebo and for VIS410 4000 mg versus 2000 mg will be presented. The number and percentage of subjects in each treatment group with clinical response will be summarized. Results will be presented graphically as well.

This analysis will be repeated for subjects with >2 vital signs abnormalities at baseline, using the same analysis algorithm described above; under this analysis, no subject will meet criteria for clinical response at baseline.

9.2.4 Time to cessation of ventilator support

Based on data from subjects on O2 support at baseline, the probability of time to cessation of ventilator support will be calculated via Kaplan-Meier based on ordinal scale data. Time to cessation of ventilator support will be calculated as Date of Event – Date of Day 1. If the event is not achieved then the value will be censored and calculated as Date of the last available ordinal assessment – Day 1. P-values for each VIS410 dose versus placebo, VIS410 total versus placebo and for VIS410 4000 mg versus 2000 mg will be presented. Results will be presented graphically as well.

9.2.5 Healthcare resource utilization

Descriptive statistics will be used to compare the total number of days in the hospital and/or ICU from admission to discharge, number of subjects requiring ICU admission post-randomization, overall number of days in the ICU, number of hours on ventilation, rehospitalization due to influenza A relapse/reinfection, the total number of days of oseltamivir therapy, and the total number of days to resumption of usual activities by treatment group.

Time (number of days) to resumption of usual activities will be determined from the VAS (scale ranged from 0 to 10, where 0 indicates subject is unable to perform any of his/her usual activities prior to influenza onset, and 10 indicates subject is able to fully perform all usual activities). Time to resumption of usual activities will be calculated as the difference between the first day the subject reports a score of 10 and Day 1. If a subject does not report a score of 10 by Day 14, a value of 14 will be used in the analysis. This evaluation will be performed using the MITT population. Additional analyses of VAS scores will reflect summaries of mean VAS scores by study day (up to Day 14), along with change from baseline and percent change from baseline will be generated; p-values will be based on ANOVA using rank transformation of VAS scores. VAS summaries will also be generated in the subsets of subjects with time from onset of symptoms to treatment < 72 hours or ≥ 72 hours. Mean VAS scores by study day along with standard deviations will be presented in figures, overall subjects and in the indicated subsets.

9.2.6 Influenza patient reported outcomes

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 Appendix 16.3.1. A description of the calculation of domain, component, and total symptom scores is presented in Appendix 16.3.2.

The FluPRO data are collected for subjects able to complete the instrument at Day 1(Baseline), then every day through Day 14. 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. Analyses of FluPRO variables will be conducted only on the subset of the MITT population who had a baseline FluPRO Questionnaire assessment.

The number and percentage of subjects with and without symptoms for each domain, component and total symptom scores will be summarized overall and for each day. In these analyses, a subject mean score >1 will be analyzed as having symptoms and a mean score less than or equal to 1 will be analyzed as not having symptoms. The number and percentage of subjects who were not able to complete the assessment at each visit will be summarized by treatment group.

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be used to compare the duration of symptoms of influenza-like illness in the subset of subjects able to complete the FluPRO Questionnaire at baseline and post-dose by treatment group. 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 and 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 defined as the earliest visit day from 2 consecutive means ≤1.0. 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 14 FluPRO survey, the subject's data will be listed as ">14" and summarized as 14 days. Treatment group comparisons will be based on Analysis of Variance (ANOVA) using rank-transformed values.

Kaplan-Meier methods will also be used to calculate the median time, 25th percentile, and 75th percentile time to resolution. P-values for each VIS410 dose versus placebo, VIS410 total versus placebo and for VIS410 4000 mg versus 2000 mg will be presented based on log-rank tests. Resolution for the total symptom score is defined as a mean score ≤1.0 and all 6 domain scores are ≤1.0. Resolution for the 6 domain scores and the 3 component scores is defined as a mean score ≤1.0.

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), with n, mean, SD, median, minimum, and maximum by treatment group, including a combined low-dose and high-dose VIS410 group. The differences for each VIS410 dose versus placebo, VIS410 total versus placebo and for VIS410 4000 mg versus 2000 mg will be tested using ANOVA based on ranks . The maximum severity of symptoms overall and on each day will be summarized for the domain, component, and total symptom scores.
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. $AUCt_{i,}\text{-}t_i\text{+}1\text{=}1/2\text{*}(S_i + S_i\text{+}1)\text{*}(t_i\text{+}1 – t_i)$ where S_i is the total symptom score at time point t_i. All time points from pre-dose to Day 14 will be considered.

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.

9.2.7 Complications of Influenza

Complications of influenza are defined as pneumonia, myocarditis, worsening of chronic bronchitis, sinusitis, otitis, other chronic pulmonary diseases, encephalopathy, and death. Complications of influenza and use of antibiotic therapy for bacterial pneumonia will be reported by variable, treatment group, and time point. The number of subjects with a diagnosis of bacterial pneumonia/superinfection will be summarized by treatment group. Diagnosis of bacterial pneumonia will be based on local clinical practice, usually an assessment of clinical features and any radiographic evidence of bacterial pneumonia (e.g., infiltrate) and/or microbiologic evidence of bacterial pneumonia.

Sponsor-defined Bacterial pneumonia based on Medical History, Concomitant Medications and Adverse Events will be summarized. The definition of two Bacterial Pneumonia parameters will be based on the following criteria:

(1) Incident Bacterial Pneumonia: defined as an adverse event of bacterial pneumonia or initiation of antibiotics Day 1 or after of greater than 2 days duration or an adverse event of pneumonia with concurrent use of antibiotics with the antibiotics initiated no more than 2 days prior to the pneumonia start date.
(2) Any Bacterial Pneumonia: defined as Incident Bacterial Pneumonia or a medical history of bacterial pneumonia that is ongoing at time of enrollment or a medical history of pneumonia that is ongoing and being treated with antibiotics on the screening date.

All-cause and attributable mortality will be evaluated on Days 14, 28 and 56. Attributable mortality will be derived from the Complication of Influenza CRF; All-Cause mortality will be derived from Complication of Influenza, Seven-Level Ordinal Scale, Adverse Event and Study Completion CRFs.

Results of diagnostic laboratory tests (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and procalcitonin results will be listed.

9.2.8 Nasopharyngeal Viral Load

Standard non-compartmental approaches using Phoenix WinNonlin (Certara, Princeton, NJ, USA; Version 7.0 or higher) will be used to calculate nasopharyngeal viral load (VL) parameters. 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 Day 7 for $TCID_{50}$ and Day 14 for qRT-PCR.

Viral shedding by qRT-PCR or $TCID_{50}$ versus time and VL AUC will be assessed using baseline-adjusted and non-adjusted comparisons. Each of the analyses described above will also be performed for the MITT subgroup comprised of all MITT subjects with a positive baseline-positive influenza viral culture result. In addition, VL and VL AUC by qRT-PCR for the first 50 subjects will be listed through Day 28 if subject is qRT-PCR positive on Day 14 and the Day 28 sample is tested by qRT-PCR (no summary statistics will be presented). For missing data on Day 1 post-dose, 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 predose, the analysis will be conducted by replacing the missing data with the Day 1 postdose observable measurement. Subjects missing both Day 1 predose and Day 1 postdose will be removed from the analysis. Some parameters will also be analyzed using baseline-adjusted values. Viral load data will be normalized by dividing the value by the baseline value.

ANOVA will be used to assess the difference between treatment groups in the VL AUC from nasopharyngeal swabs based on qRT-PCR and $TCID_{50}$. If the assumptions needed for ANOVA are not met, log transformation and/or non-parametric methods will be used. Differences between groups in peak post-baseline VL (qRT-PCR and $TCID_{50}$) will be tested, and the proportion of subjects with peak VL (by qRT-PCR and $TCID_{50}$) occurring post-baseline.

Several methods will be considered to assess the potential impact of baseline viral load (qRT-PCR and TCID50) on viral load AUC. Division of AUC by baseline viral load followed by ANOVA will be used as an initial measure of baseline viral load impact. In addition, an ANCOVA model may be used. The model will be evaluated with treatment as a fixed effect and baseline viral load as a continuous covariate. Each VIS410 dose group and the combined VIS410 total group will be compared to placebo.

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.

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.

A list of viral load parameters in respiratory samples that may be assessed (MITT population and subgroups) includes:

- Peak virus concentration by qRT-PCR
- Viral nasopharyngeal qRT-PCR AUC, BL to Day 5 and BL to Day 7 (baseline-adjusted and non-adjusted comparisons)
- Viral shedding by qRT-PCR versus time (baseline-adjusted and non-adjusted comparison)
- Percentage of subjects in whom peak qRT-PCR value occurred post-baseline
- Viral nasopharyngeal qRT-PCR AUC, BL to Day 7 and BL to Day 14
- Peak virus concentration by $TCID_{50}$
- Percentage of subjects in whom peak $TCID_{50}$ value occurred post-baseline Viral nasopharyngeal $TCID_{50}$ AUC, BL to Day 5 and BL to Day 7

- For $TCID_{50}$ AUC analyses (both the MITT population and the MITT population subset comprised of subjects with positive BL nasopharyngeal viral cultures); baseline-adjusted and non-adjusted comparisons.
- Viral shedding by $TCID_{50}$ versus time (baseline-adjusted and non-adjusted comparison)
- Percentage of subjects with negative viral cultures by nominal study day (Day 3, Day 5, Day 7) (both the MITT population, and the MITT population subset comprised of subjects with positive BL nasopharyngeal viral cultures)
- Kaplan Meier analysis of time to resolution (negative) of viral cultures, by treatment arm (both the MITT population, and the MITT population subset comprised of subjects with positive BL nasopharyngeal viral cultures
- Additional subset analyses will examine the above outcomes by:
    - Virus strain family, H1N1 versus H3N2
    - Duration of symptoms prior to treatment (< 72 hours, ≥ 72 hours)
    - Geographic region of enrollment

9.2.9 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 [redacted] 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 $TCID_{50}$ will be imputed to zero.

$TCID_{50}$ example:

- If the database contains [redacted] the following rules will be used for calculating parameters
    - [redacted]
    - [redacted]

9.2.10 Time to Resolution of Viral Load

Two analyses of median time to resolution of viral load, as determined by qRT-PCR or $TCID_{50}$ results, and the 95% CI about the median, will be presented using Kaplan-Meier methods. Additional exploratory statistical analyses will be conducted to determine the differences in Kaplan-Meier curves using a log-rank test. Time to resolution of viral load will be assessed on all samples in the MITT population collected through the Day 7 visit for $TCID_{50}$ analysis and

through the Day 14 visit for qRT-PCR analysis. For missing data on Day 1 post-dose, 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 predose, the analysis will be conducted by replacing the missing data with the Day 1 post-dose observable measurement. Subjects missing both Day 1 predose and Day 1 post-dose 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 load 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 the Day 7 ($TCID_{50}$) or Day 14 (PCR) visit
    - If virus is still above level of detection at Day 7 ($TCID_{50}$) or Day 14 (PCR) visit, the value will be censored the on Day 7 visit for $TCID_{50}$ or Day 14 (PCR)
- Time to resolution of viral load 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 the Day 7 ($TCID_{50}$) or Day 14 (PCR) visit
    - If virus is still above level of detection at Day 7 ($TCID_{50}$) or Day 14 (PCR) visit, the value will be censored the on Day 7 visit for $TCID_{50}$ or Day 14 (PCR)

The above analysis will also be performed for the MITT subset comprised of subjects with a positive baseline viral culture based on TCID50.

10 PHARMACOKINETIC ANALYSES

Standard non-compartmental approaches using Phoenix WinNonlin (Certara USA, 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. Values below the BLQ will be set to 0. 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} (ng/ml): maximum observed concentration
- T_{max} (day): time of C_{max}
- T_{last} (day): time of the last measurable concentration
- $AUC_{0-\infty}$ (day*ug/mL): area under the concentration-time curve from time 0 extrapolated to infinity
- $AUC_{\%extrap}$ (%): percent extrapolated to $AUC_{0-\infty}$
- AUC_{0-last} (day*ug/mL): area under the concentration-time curve from time 0 to the last measurable concentration

- $t_{1/2}$ (day): terminal elimination half-life
- CL (ml/day): total clearance (serum only)
  V_d (ml): volume of distribution (serum only) Ratio of nasal: serum AUC in subjects with both values available. The nasal:serum ratio will be calculated with both $AUC_{0\text{-last}}$ and with $AUC_{0\text{-}\infty}$

Additional PK parameters may be determined as appropriate.

Plasma and nasal concentration data will be analyzed using Phoenix 7.0 or higher. Individual time points for the terminal slope will automatically be selected by the software, and linear-linear interpolation calculation method will be used for the analysis. No value for $t_{1/2}$ or other terminal slope dependent parameters (ex. $AUC_{0\text{-}\infty}$ and CL) will be reported for concentration profiles that do not exhibit an elimination phase in individual concentration versus time profiles (at least 3 concentration measurements following Cmax) or if the fit of the terminal slope data is poor (i.e., if adjusted R2 <0.800 for the log-linear regression analysis of λz). If the extrapolated portion of AUCinf from time of last measurable plasma concentration to infinity (AUC%extrap) for a subject is greater than 20.0%, the $AUC_{0\text{-}\infty}$ related PK parameters (ex. CL and V_d) will be excluded. No imputation for missing PK data will be performed. BLQ PK samples prior to T_{max} will be set to 0 in the NCA analysis datasets. All BLQ PK samples following T_{max} will be set to missing in the analysis dataset.

10.1 Serum Pharmacokinetics

Serum concentrations will be listed by subject for VIS410 and summary statistics by group will be presented, including means, geometric means, SDs, coefficient of variation (CV), medians, and ranges, as appropriate. Summary graphs, including mean concentration-time profiles by group, will also be presented. Noncompartmental PK parameters will be summarized by group and displayed graphically. The serum concentration data may also be analyzed by population PK methods using nonlinear mixed effects modeling as implemented in NONMEM or equivalent software. Population PK analysis will be performed to describe the time course of serum concentrations of VIS410, and may be pooled with data from prior studies. The influence of covariates on PK parameters will be investigated, if necessary and appropriate.

Additional analyses and summaries may be generated as appropriate.

Results of population PK or PK/PD analyses may be reported outside the CSR

10.2 Pharmacokinetics of Nasopharyngeal Secretions and Tracheal Aspirate

Nasopharyngeal swabs will be obtained from both nostrils (1 swab per nostril). The first 50 randomized subjects will have nasopharyngeal swabs collected up to Day 56 (predose, end of infusion, Days 3, 5, 7, 14, 28 and 56); while in the remaining subjects, nasopharyngeal swabs will be obtained up to Day 14 only. If the subject remains in the hospital on Day 10, then additional nasopharyngeal swabs will be obtained on Day 10. Tracheal aspirates will be collected only if subject is intubated and only obtained at Day 1 pre-dose, post-dose, Day 3, Day 5, and Day 7 or at other timepoints per investigator's request. The VIS410 concentrations in the nasopharyngeal secretions and tracheal aspirate will be listed by subject, and summary statistics by group will be reported as described for the serum concentrations. Values less than the BLQ

will be set to 0. The computed noncompartmental PK parameters will be listed by subject for VIS410. Summary statistics and PK parameters will be presented, including means, geometric means, standard deviations, CV, medians, and ranges, as appropriate. Summary graphs, including mean concentration-time profiles by group, will also be presented. The nasopharyngeal concentration data may also be analyzed by population PK methods using nonlinear mixed effects modeling as implemented in NONMEM or equivalent software. If necessary, the data may be pooled with data from previous studies for the nonlinear mixed effects (NLME) modeling only. Additional analyses and summaries may be generated as appropriate. Results of population PK or PK/PD analyses may be reported outside the CSR.

11 OTHER SECONDARY 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 "5". Values that are <10 (LLOQ) will be assessed as 5 and values >10240 (ULOQ) will be assessed as 10240. If baseline serum samples are not available for HAI titration, Day 3 values may be imputed back to baseline, if HAI $\leq$ 40.

11.2 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 separate genotypic report and a phenotypic report.

11.3 Exploratory Pharmacokinetic/Pharmacodynamic Analyses

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

- Viral Load AUC ($TCID_{50}$ and qRT-PCR)
- Post-Baseline Peak Duration of viral shedding ($TCID_{50}$, qRT-PCR)
- Proportion of subjects with undetectable viral load by group and study day (TCID50, qRT-PCR)
- Proportion of subjects with undetectable viral load by group and study day (TCID50), among the MITT subset of subjects with positive viral culture results at Baseline.

The independent variables (PK exposure parameters) will include serum VIS410 AUC and C_{max}. 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.

11.4 Exploratory Analysis of PK and Virology in Tracheal Aspirates

Exploratory analyses will be performed to evaluate the difference in VL (qRT-PCR and $TCID_{50}$) between VIS410 + oseltamivir and oseltamivir alone treatment groups in tracheal aspirates. VL (qRT-PCR and $TCID_{50}$) will be compared between nasopharyngeal samples and tracheal aspirates obtained from the same subjects. VIS410 concentrations (PK) will be compared in serum, nasopharyngeal, and tracheal aspirates obtained from the same subjects. Relationships between VIS410 and viral load in tracheal aspirates may also be assessed.

11.5 Exploratory Analysis of PK and Anti-drug Antibodies (ADA)

Exploratory analyses will be performed to evaluate the following serum and nasopharyngeal endpoints by ADA status:

- C_{max} (ng/ml)
- T_{max} (day)
- T_{last} (day)
- $AUC_{0-\infty}$ (day*ug/mL)
- $AUC_{\%extrap}$ (%)
- AUC_{0-last} (day*ug/mL)
- $t_{1/2}$ (day)
- CL (ml/day) (serum only)
- V_d (ml) (serum only)

11.6 Anti-drug Antibodies

Summaries of anti-VIS410 antibody titers will be presented by treatment group and time point using descriptive statistics. Anti-VIS410 antibody titer results will be summarized as negative/positive; the ADA positive category includes subjects with >4 fold change, the ADA negative category includes subjects with no more than a 4-fold change from baseline. Overall positivity will be based on the subject being ADA positive at any post-baseline timepoint; negativity will be based on the subject being ADA negative at all assessed post-baseline timepoints.

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 20.1.

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 and percentages 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. The difference in proportions between treatment groups in each of these categories will be calculated.

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.
-
- Anaphylaxis and hypersensitivity reactions will be determined by clinical evaluation of TEAEs per the Safety Plan prior to database lock. For input into analysis, a spreadsheet of subjects meeting the definition of either or both of these types of events will be generated and finalized prior to database lock.
- 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: North America (Canada and US), South Africa, Asia and Oceania (Australia, Malaysia, New Zealand, Singapore, and Thailand), and Europe (Belarus, Belgium, Bulgaria, Estonia, France, Georgia, Latvia, Russia, Serbia, Spain, Ukraine and Georgia))

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, TEAEs leading to death and TEAEs occurring in at least 5% of the subjects in any treatment group. 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.

All adverse event data will be listed by subject (in order of adverse event start date).

12.2 Clinical Laboratory Tests

Hematology, blood chemistry, and urinalysis data are collected at Screening, Day 5, Day 14, Day 28, and Day 56/Early Termination. They will be summarized by treatment group at each visit, as well as change from Baseline for continuous parameters at post-baseline visits.

- Hematology and Coagulation: hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) with differential, lymphocytes, monocytes, neutrophils, eosinophils, basophils, platelets, partial thromboplastin time, 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).

- Chemistry: 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, 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, troponin, tryptase, and chymase 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 16.4, 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 3, Day 5, Day 7, Day 14, Day 28, Day 56/Early termination. During hospitalization, vital signs will be measured at the end of the infusion on Day 1 and then BID (preferably at the same time each day) up until Day 14 or discharge from the hospital if this occurs prior to Day 14.

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 16.5. A listing of the subjects meeting PCS criteria will also be provided.

All vital signs data will be listed.

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.

12.6 Radiological Assessment

A baseline chest x-ray or CT scan will be performed for the assessment of pneumonia. However, a chest x-ray or CT scan performed as part of routine standard of care within 72 hours before randomization will be acceptable. Chest x-ray and/or CT scan results will be listed.

13 INTERIM ANALYSIS

13.1 Data Safety Monitoring Board review

A DSMB will be empaneled to monitor the safety of the enrolled subjects. Safety data is scheduled to be reviewed after 30 subjects and subsequently, approximately 70 subjects have completed study Day 14. 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\1020Visterra\Stats\Programs\xxx.sas" left justified and "Date-Time: DDMMMYYYY:HH:MM" right justified

15 REFERENCE LIST

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

16 APPENDICES

16.1 Changes to the Protocol Specified Analyses

- Due to the exploratory nature of the study, it was decided that the Per Protocol population would not be defined.
- The definition of the MITT population does not include the requirement of a post-baseline assessment of O_2.
- 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.
- Due to the change in focus of the primary efficacy endpoint, the addition of the 5 point ordinal scale was added

Visterra, Inc.
SAP for Protocol VIS410-203 January 17, 2019

16.2 Schedule of Assessments

Study Time Point	Screening[1]	Day 1				Day 3	Day 5 (± 1)	Day 7 (± 1)	Day 14 (± 3)	Day 28 (± 3)	Day 56 (± 7)
		Baseline	Predose	0 Hour	End of Infusion						LFU/ET Visit[2]
Screening/Administrative Assessments											
Informed consent	X										
Inclusion/exclusion criteria	X										
Medical history and demographics	X										
Nasopharyngeal swab for rapid flu test[3]	X										
Onset of symptoms interview	X										
Prior medications[4]	X	X									
Randomization[5]		X									
Subject Diary[6]		X—	—	—	—	—	—	—	—	—	—X
Safety Assessments [7]											
Supine ECG[8]	X	X[9]			X						
Vital signs[10]	X	X[9]	X		X	X	X	X	X	X	X
SpO_2[11]	X	X[9]	X		X—	—	—	—	—	—X	
Body temperature[12]	X	X[9]	X		X	X	X	X	X	X	X
Physical exam[13]	X										
FluPRO Questionnaire[14]		X—	—	—	—	—	—	—	—X		
Seven-Level ordinal scale[15]		X—	—	—	—	—	—	—	—X		
Pregnancy test[16]	X	X[17]									X
Chemistry, hematology, urinalysis[18,19]		X					X		X	X	X
Serum creatinine[20]	X										
C-reactive protein (CRP)		X					X				
Erythrocyte sedimentation rate (ESR)[20a]		X					X		X		
Chest x-ray / CT scan[21]	X										
Procalcitonin		X									
AEs, SAEs, and AESIs		X—	—	—	—	—	—	—	—	—	—X
Concomitant therapy		X—	—	—	—	—	—	—	—	—	—X

Study Time Point	Screening[1]	Day 1				Day 3	Day 5 (± 1)	Day 7 (± 1)	Day 14 (± 3)	Day 28 (± 3)	Day 56 (± 7)
		Baseline	Predose	0 Hour	End of Infusion						LFU/ET Visit[2]
Influenza complications		X—	—	—	—	—	—	—	—	—	—X
VAS for assessment of resumption of normal activities		X—	—	—	—	—	—	—	—	—	—X
Healthcare utilization[22]		X—	—	—	—	—	—	—	—	—	—X
Study Agent Administration/Virologic/PK, and Immunology Assessments											
Pretreatment medications 60 minutes (± 5 min) prior to start of infusion[23]			X								
VIS410/placebo infusion[24]				X							
Oseltamivir therapy[25]				X—	—	—	—X				
Serum PK		X			X[26]		X		X	X	X
Nasopharyngeal swab[27,28]			X		X[26]	X	X	X	X	X	X
Tracheal aspirate[29]			X		X	X	X	X			
Serum ADA		X								X	X
Serum HAI sample		X								X	

[1] Screening and baseline activities may be performed on the same day.
[2] Subjects who terminate the study participation early are encouraged to have all follow-up safety assessments done at the time of study termination. All other subjects will return for a final follow-up visit at Day 56 ± 7 days.
[3] Single nasopharyngeal swab will be obtained from one nostril for influenza A rapid test. This screening test is not necessary if the subject has a prior influenza A positive test by Rapid Antigen Test or with another commercially available test including PCR, FIA, or ELISA within the prior 48 hours of screening.
[4] Collect all medications taken, including over-the-counter, within 7 days prior to VIS410/placebo administration.
[5] Randomization will be stratified by presence or absence of positive pressure ventilation (PPV) at baseline to ensure an even distribution across treatment arms.
[6] Subject diary will be provided upon discharge from the hospital and will record daily oseltamivir dosing (as applicable) and will have a daily VAS for assessing resumption of usual activities until either the subject reports that all usual activities (prior to influenza onset) can be performed or Day 56, whichever comes first. In addition, the Influenza Patient Reported Outcomes (FluPRO) Questionnaire will be provided and completed daily up until Day 14 (if applicable).
[7] Additional safety assessments may be performed outside of the defined protocol criteria, at the Investigator's discretion.
[8] Single 12-lead ECG will be performed after a 5-minute rest in supine position.
[9] To be repeated only if screening and baseline visits are more than 24 hours apart.

[10] Vital signs should be measured after 5 minutes of rest in a supine position and include heart rate, respiratory rate, and blood pressure. During hospitalization, vital signs will be measured at the end of the infusion on Day 1 and then BID (preferably at the same time each day) up until Day 14 or discharge from the hospital if this occurs prior to Day 14.

[11] Baseline SpO_2 on room air to be documented, if available. Once randomized, SpO_2 to be measured using pulse oximetry 3 times daily (approximately every 8 hours) at approximately the same time each day until stable. Stable SpO_2 is defined as two consecutive SpO_2 values of > 92% on room air that are at least 8 hours apart.

[12] During hospitalization, body temperature will be recorded at the end of infusion on Day 1 then BID up until Day 14 or discharge from the hospital if discharge occurs prior to Day 14. In cases where obtaining oral temperature is not possible, core temperature will be obtained. While hospitalized, the maximum temperature should be recorded for each 12-hour interval (from 12 AM to 12 PM and from 12 PM to 12 AM).

[13] Additional targeted physical exam may be performed throughout the study as needed at the Investigator's or his/her designee's discretion.

[14] The Influenza Patient Reported Outcomes (FluPRO) Questionnaire (Appendix 14.1) must be completed (ie, self-reported) by the subject at baseline (Day 1) and daily thereafter through Day 14. Subjects who are not able to complete the questionnaire at baseline (Day 1) will be exempt from this assessment throughout the study. The FluPRO will be completed at home for subjects that are discharged from the hospital prior to Day 14.

[15] The ordinal scale will be completed from baseline (Day 1) and daily thereafter through Day 14. For each day, subjects will be classified by the worst clinical outcome for which they qualify.

[16] A urine or serum pregnancy test must be performed at screening locally (ie, by the investigative site) within 2 days prior to dosing. Negative results must be obtained prior to randomization.

[17] A serum pregnancy test will be performed at the central lab for all female subjects of childbearing potential following randomization at baseline

[18] Subjects to be enrolled based on the Investigator's discretion including any local laboratory results per SOC at institution.

[19] See Laboratory Assessments for list of tests to be performed by the Central Lab in Appendix 14.2.

[20] Serum creatinine to be done locally within 24 hours prior to randomization, the result is required for oseltamivir dosing.

[20a] ESR to be performed locally.

[21] A chest x-ray or computed tomography (CT) scan taken per SOC within 72 hours before dosing is acceptable.

[22] Healthcare utilization (total length of hospital stay, length of ICU stay, and rehospitalization) will be captured through the last follow-up visit.

[23] If the subject has any history of delayed gastric emptying, including premenstruation syndrome or menstruation, he or she may receive oral premedications 120 minutes prior to IV VIS410/placebo infusion.

[24] VIS410/placebo will be administered over 2 hours. Infusion time can be extended to up to 4 hours at discretion of the Investigator only if local infusion site–related symptoms occur.

[25] Minimum of 10 doses of oseltamivir treatment (BID for 5 days) is required. Treatment with oseltamivir may be extended for up to 5 additional days (up to 20 doses of total therapy) if clinical symptoms warrant further treatment as assessed by the Investigator. Note: based on SOC, subjects may have started oseltamivir therapy prior to randomization. For patients unable to swallow, oseltamivir capsules can be opened and mixed with liquid for ease of administration.

[26] To be obtained up to 2 hours post-VIS410 administration.

[27] Nasopharyngeal swabs will be obtained for virology and/or PK from both nostrils (1 swab per nostril). The first 50 randomized subjects will have nasopharyngeal swabs collected up to Day 56 (predose, end of infusion, Days 3, 5, 7, 14, 28 and 56); while in the remaining subjects, nasopharyngeal swabs will be obtained up to Day 14 only.

[28] If the subject remains in the hospital on Day 10, additional nasopharyngeal swabs will be obtained on Day 10.

[29] One tracheal aspirate sample for virology and PK will be obtained (ventilated subjects only).

16.3 FluPRO Questionnaire

16.3.1 Individual Questions

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.

16.3.2 Calculation of Domain, Component and Total Symptom Scores

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

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/ mm^3	750-999/ mm^3	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
LS: 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 Region 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
14.1.7.1	Treatment Exposure and Compliance	Safety
14.1.7.2	Treatment Exposure and Compliance	MITT
14.2.1.1.1	Summary of Clinical Outcome on Seven-Level Ordinal Scale through Day 14	MITT
14.2.1.1.2	Summary of Clinical Outcome on Five-Level Modified Ordinal Scale through Day 14	MITT
14.2.1.1.3	Summary of Clinical Outcome on Seven-Level Ordinal Scale through Day 14 Sensitivity Analysis	MITT
14.2.1.2	Summary of Area Under the Curve for Seven-Level Ordinal Scale	MITT
14.2.1.3	Summary of Area Under the Curve for Seven-Level Ordinal Scale Excluding Death Outcome	MITT
14.2.1.4	Summary of Area Under the Curve based on Modified Five-Level Ordinal Scale	MITT
14.2.1.5	Summary of Area Under the Curve for Seven-Level Ordinal Scale Sensitivity Analysis	MITT
14.2.1.6	Additional Assessments for Seven-Level Ordinal Scale	MITT
14.2.1.7	Additional Assessments for Seven-Level Ordinal Scale Sensitivity Analysis	MITT
14.2.1.8	Summary of Proportions of Best and Worst Cases for Seven-Level and Modified Five-Level Ordinal Scale	MITT
14.2.2.1	Time to Cessation of O2 Support	MITT
14.2.3.1.1	Kaplan-Meier Estimates of Time to Clinical Response (Resolution of Vital Signs)	MITT
14.2.3.1.2	Kaplan-Meier Estimates of Time to Clinical Response (Resolution of Vital Signs) in Subjects with > 2 Vital Sign Abnormalities at Baseline	MITT

14.2.3.1.3	Kaplan-Meier Estimates of Time to Complete Clinical Response (Resolution of Vital Signs)	MITT
14.2.3.1.4	Kaplan-Meier Estimates of Time to Complete Clinical Response (Resolution of Vital Signs) in Subjects with >2 Vital Sign Abnormalities at Baseline	MITT
14.2.4.1	Kaplan-Meier Estimates of Time to Cessation of Ventilator Support	MITT
14.2.5.1	Summary of Healthcare Resource Utilization Parameters	MITT
14.2.5.2	Summary of Visual Analogue Scale Scores	MITT
14.2.6.1.1	Descriptive Summary of FluPRO Domain Scores, Component Scores, and Total Score	MITT
14.2.6.2.1	Proportion of Subjects With and Without Symptoms Measured by FluPRO for Symptoms, Domain Scores, Component Scores, and Total Score	MITT
14.2.6.3.1	Summary of FluPRO Duration of Symptoms	MITT
14.2.6.4.1	Summary of FluPRO Symptoms by Maximal Severity	MITT
14.2.6.5.1	Summary of FluPRO Area Under the Curve for Domain Scores, Component Scores, and Total Score by Mean	MITT
14.2.6.6.1	Kaplan-Meier Estimates of FluPRO Time to Symptom Resolution for Total, Domain and Component Scores	MITT
14.2.6.7.1	Kaplan-Meier Estimates of Duration of Influenza Symptoms for Total, Domain and Component Scores	MITT
14.2.7.1	Influenza Symptom Complications	MITT
14.2.7.2	Bacterial Pneumonia (Derived)	MITT
14.2.8.1	Summary of Mortality Rates	Safety
14.2.8.2	Summary of Mortality Rates	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
14.3.1.4.1	Summary of Treatment-emergent Adverse Events Occurring in >=5% of Subjects in Any Treatment Group	Safety
14.3.1.4.2	Summary of Treatment-emergent Adverse Events Occurring in >=2% 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 Grade	Safety
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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 Grade	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	Vital Signs - Summary and Change from Baseline	Safety
14.3.5.10	Vital Signs – Summary of Not Done, Normal, Abnormal, and Clinically Significant	Safety
14.3.5.11	Vital Signs – Shift Tables of Not Done, Normal, Abnormal, and Clinically Significant	Safety
14.3.5.12	Summary of PCS Vital Sign Values	Safety
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14.3.5.14	Electrocardiogram - Summary of Normal and Abnormal Results	Safety
14.3.5.15	Electrocardiogram – Shift Table of Normal and Abnormal Results	Safety
14.3.5.16	Electrocardiogram – Categorical Summary of QTcF Changes	Safety
14.3.5.17	Physical Examination at Baseline Summary	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 Serum VIS410 Pharmacokinetic Parameters by ADA Status	PK
14.4.1.4	Summary of Nasopharyngeal VIS410 Concentrations	PK
14.4.1.5	Summary of Nasopharyngeal VIS410 Pharmacokinetic Parameters	PK

14.4.1.6	Summary of Nasopharyngeal VIS410 Pharmacokinetic Parameters by ADA Status	PK
14.4.1.7	Summary of Tracheal Aspirate VIS410 Concentrations	PK
14.4.1.8	Summary of Tracheal Aspirate VIS410 Pharmacokinetic Parameters	PK
14.4.2.1	Summary of Anti-influenza A Antibodies	MITT
14.4.2.2.1.1	Peak Viral Load (VL) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14	MITT
14.4.2.2.1.2	Peak Viral Load (VL) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 by Subtype	MITT
14.4.2.2.1.3	Peak Viral Load (VL) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.2.1.4	Peak Viral Load (VL) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 Baseline Adjusted	MITT
14.4.2.2.2.1	Peak Viral Load (VL) Based on TCID50 from Nasopharyngeal Swabs Through Day 7	MITT
14.4.2.2.2.2	Peak Viral Load (VL) Based on TCID50 from Nasopharyngeal Swabs Through Day 7 by Subtype	MITT
14.4.2.2.2.3	Peak Viral Load (VL) Based on TCID50 from Nasopharyngeal Swabs Through Day 7 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.2.2.4	Peak Viral Load (VL) Based on TCID50 from Nasopharyngeal Swabs Through Day 7 Baseline Adjusted	MITT
14.4.2.3.1.1	Area Under the Viral Load-Time Curve (VL AUC) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14	MITT
14.4.2.3.1.2	Area Under the Viral Load-Time Curve (VL AUC) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 by Subtype	MITT
14.4.2.3.1.3	Area Under the Viral Load-Time Curve (VL AUC) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.3.1.4	Area Under the Viral Load-Time Curve (VL AUC) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 Baseline Adjusted	MITT
14.4.2.3.1.5	Area Under the Viral Load-Time Curve (VL AUC) Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 using Imputation	MITT

14.4.2.3.2.1	Area Under the Viral Load-Time Curve (VL AUC) Based on TCID50 from Nasopharyngeal Swabs Through Day 7	MITT
14.4.2.3.2.2	Area Under the Viral Load-Time Curve (VL AUC) Based on TCID50 from Nasopharyngeal Swabs Through Day 7 by Subtype	MITT
14.4.2.3.2.3	Area Under the Viral Load-Time Curve (VL AUC) Based on TCID50 from Nasopharyngeal Swabs Through Day 7 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.3.2.4	Area Under the Viral Load-Time Curve (VL AUC) based on TCID50 from Nasopharyngeal Swabs Through Day 7 Baseline Adjusted	MITT
14.4.2.3.2.5	Area Under the Viral Load-Time Curve (VL AUC) based on TCID50 from Nasopharyngeal Swabs Through Day 7 using Imputation	MITT
14.4.2.4.1	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by qRT-PCR Through Day 14	MITT
14.4.2.4.2	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by qRT-PCR Through Day 14 by Subtype	MITT
14.4.2.4.3	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by qRT-PCR Through Day 14 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.5.1	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by TCID50 Through Day 7	MITT
14.4.2.5.2	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by TCID50 Through Day 7 by Subtype	MITT
14.4.2.5.3	Kaplan-Meier Estimates of Median Time to Resolution of Viral Load Measured by TCID50 Through Day 7 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.6.1	Percent of Subjects Negative for Viral Titer by Study Day Determined by qRT-PCR	MITT
14.4.2.6.2	Percent of Subjects Negative for Viral Titer by Study Day Determined by qRT-PCR by Subtype	MITT
14.4.2.6.3	Percent of Subjects Negative for Viral Titer by Study Day Determined by qRT-PCR Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.7.1	Percent of Subjects Negative for Viral Titer by Study Day Determined by TCID50	MITT
14.4.2.7.2	Percent of Subjects Negative for Viral Titer by Study Day Determined by TCID50 by Subtype	MITT

14.4.2.7.3	Percent of Subjects Negative for Viral Titer by Study Day Determined by TCID50 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.8.1.1	Viral Load by Visit Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14	MITT
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14.4.2.8.1.3	Viral Load by Visit Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.8.1.4	Viral Load by Visit Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 Baseline Adjusted	MITT
14.4.2.8.1.5	Viral Load by Visit Based on qRT-PCR from Nasopharyngeal Swabs Through Day 14 using Imputation	MITT
14.4.2.8.2.1	Viral Load by Visit Based on TCID50 from Nasopharyngeal Swabs Through Day 7	MITT
14.4.2.8.2.2	Viral Load by Visit Based on TCID50 from Nasopharyngeal Swabs Through Day 7 by Subtype	MITT
14.4.2.8.2.3	Viral Load by Visit Based on TCID50 from Nasopharyngeal Swabs Through Day 7 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.8.2.4	Viral Load by Visit Based on TCID50 from Nasopharyngeal Swabs Through Day 7 Baseline Adjusted	MITT
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14.4.2.9.1	Proportion Peak VL Observed Post-Baseline Based on qRT-PCR and TCID50	MITT
14.4.2.9.2	Proportion Peak VL Observed Post-Baseline Based on qRT-PCR and TCID50 by Subtype	MITT
14.4.2.9.3	Proportion Peak VL Observed Post-Baseline Based on qRT-PCR and TCID50 Subjects Positive for Viral Titer at Baseline	MITT
14.4.2.10.1	Summary of Anti-VIS410 Antibody Titer Positive Versus Negative	MITT
14.4.2.10.2	Summary of Anti-VIS410 Antibody Titer Fold Increase from Baseline	MITT
14.4.2.10.3	Summary of Anti-VIS410 Antibody Titers in Categories	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 Analysis Populations	All Subjects
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	Safety
16.2.4.5	Positive Pressure Ventilation	ITT
16.2.4.6	Nasopharyngeal Swab for Flu Test at Screening	ITT
16.2.5.1	Pretreatment Medications	ITT
16.2.5.2	Study Medication Administration and Accountability	Safety
16.2.6.1	O2 Support	MITT
16.2.6.2	Clinical Response	MITT
16.2.6.3	Ventilator Support	MITT
16.2.6.4	Healthcare Resource Utilization	MITT
16.2.6.5.1	FluPRO Questionnaire and Compliance for Individual Questions and Total Symptom Scores	MITT
16.2.6.5.2	FluPRO Questionnaire Domain Symptom Questions and Symptom Scores	MITT
16.2.6.5.3	FluPRO Questionnaire Composite Symptom Questions and Symptom Scores	MITT
16.2.6.4.5	FluPRO Duration and Severity of Symptoms	MITT
16.2.6.5.5	FluPRO Questionnaire Compliance Information	MITT
16.2.6.6	Clinical Outcome on Seven-Level Ordinal Scale	MITT
16.2.6.7	Clinical Outcome on Five-Level Ordinal Scale	MITT
16.2.7.1	Adverse Events	Safety
16.2.7.2	Influenza Complications and Derived Bacterial Pneumonia	MITT
16.2.8.1	Hematology Laboratory	Safety
16.2.8.2	Chemistry Laboratory	Safety
16.2.8.3	Urinalysis Laboratory	Safety
16.2.8.4.1	Clinical Laboratory Test Results Outside the Reference Ranges	Safety
16.2.8.4.2	Subjects with >2 category shift in DMID grades	Safety
16.2.8.5.1	Vital Signs	Safety

16.2.8.5.2	Subjects who met PCS Vital Sign Criteria	Safety
16.2.8.6.1	Electrocardiogram Data	Safety
16.2.8.6.2	Subjects with QTcF Changes	Safety
16.2.8.7	Physical Exam Data	Safety
16.2.8.8	Radiologic Assessment	Safety
16.2.9.1	Individual Listing and Summary of Virus Type by Subject	ITT
16.2.9.2	Individual Listing and Summary of Serum VIS410 Concentrations by Nominal Time Point	PK
16.2.9.3	Individual Listing and Summary of Serum VIS410 Pharmacokinetic Parameters	PK
16.2.9.4	Individual Listing and Summary of Nasopharyngeal VIS410 Concentrations by Nominal Time Point	PK
16.2.9.5	Individual Listing and Summary of Nasopharyngeal VIS410 Pharmacokinetic Parameters	PK
16.2.9.6	Individual Listing and Summary of Tracheal Aspirate Concentrations VIS410 by Nominal Timepoint	PK
16.2.9.7	Individual Listing and Summary of Tracheal Aspirate VIS410 Pharmacokinetic Parameters	PK
16.2.9.8	Individual Listing and Summary of Nasopharyngeal qRT-PCR Viral Load by Nominal Time Point	MITT
16.2.9.9	Individual Subject Peak Viral Load (VL) and Area Under the Viral Load-Time Curve (VL AUC) in Nasopharyngeal Samples Measured by qRT-PCR	MITT
16.2.9.10	Change from Baseline Nasopharyngeal Viral Shedding [qRT-PCR] by Treatment Group	MITT
16.2.9.11	Individual Listing and Summary of Nasopharyngeal TCID50 by Nominal Time Point	MITT
16.2.9.12	Individual Subject Peak Viral Load and Viral Load AUC in Nasopharyngeal Samples Measured by TCID50	MITT
16.2.9.13	Change from Baseline Nasopharyngeal Viral Shedding [TCID50] by Treatment Group	MITT
16.2.9.14	Individual Listing and Summary of Tracheal Aspirate qRT-PCR Viral Load by Nominal Time Point	MITT
16.2.9.15	Individual Listing and Summary of Tracheal Aspirate TCID50 Viral Load by Nominal Time Point	MITT
16.2.10.1	Immunogenicity Data - ADA	PK
16.2.10.2	Immunogenicity Data - HAI	MITT

16.6.3 Figures

Figure	Title	Population
14.2.1.1.1	Kaplan-Meier Plot of Time to Clinical Response	MITT
14.2.1.1.2	Kaplan-Meier Plot of Time to Complete Clinical Response	MITT
14.2.1.1.3	Kaplan-Meier Plot of Time to Complete Clinical Response in Subjects with >2 Vital Sign Abnormalities at Baseline	MITT
14.2.2.1	Kaplan-Meier Plot of Time to Cessation of Ventilator Support	MITT
14.2.3.1	Kaplan-Meier Plot of Time to Resolution of Symptoms measured by FluPRO	MITT
14.2.4.1	Kaplan-Meier Plot of Duration of Symptoms Measured by FluPRO	MITT
14.2.5.1	FluPRO Mean (± SD) Total, Domain and Component Scores by Day	MITT
14.2.5.2	Visual Analogue Scale Scores by Day	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	qRT-PCR Mean Change from Baseline in Viral Shedding versus Time	MITT
14.4.1.5	$TCID_{50}$ Median Viral Shedding versus Time Profiles	MITT
14.4.1.6	$TCID_{50}$ Mean Viral Shedding versus Time Profiles	MITT
14.4.1.7	Individual Subject $TCID_{50}$ Viral Shedding versus Time Profiles	MITT
14.4.1.8	$TCID_{50}$ Mean Change from Baseline in Viral Shedding versus Time	MITT
14.4.1.9.1	Duration of Viral Shedding Measured by qRT-PCR from End of Infusion (Days)	MITT
14.4.1.9.2	Duration of Viral Shedding Measured by qRT-PCR from Onset of Symptoms (Days)	MITT
14.4.1.10.1	Duration of Viral Shedding Measured by $TCID_{50}$ from End of Infusion (Days)	MITT
14.4.1.10.2	Duration of Viral Shedding Measured by $TCID_{50}$ from Onset of Symptoms (Days)	MITT
14.4.1.11.1	Percentage of Subjects with Negative Virology ($TCID_{50}$) by Study Day	MITT
14.4.1.11.2	Percentage of Subjects with Negative Virology ($TCID_{50}$) by Study Day Excluding Subjects Negative at Day 1	MITT
14.4.1.12	HAI Titer to Influenza A for Subjects Infected with Influenza A	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
14.4.4.1	Individual Subject Tracheal Aspirate VIS410 Concentration versus Time Profiles (linear and log-linear scales)	PK
14.4.5.1.1	Viral Shedding vs Time Unadjusted qPCF	MITT
14.4.5.1.2	Viral Shedding vs Time Unadjusted qPCF BL positive	MITT
14.4.5.1.3	Viral Shedding vs Time qPCF Baseline Adjusted	MITT
14.4.5.1.4	Viral Shedding vs Time qPCF Baseline Adjusted BL positive	MITT
14.4.5.2.1	Viral Shedding vs Time Unadjusted TCID50	MITT
14.4.5.2.2	Viral Shedding vs Time Unadjusted TCID50 BL positive	
14.4.5.2.3	Viral Shedding vs Time TCID50 Baseline Adjusted	MITT
14.4.5.2.4	Viral Shedding vs Time TCID50 Baseline Adjusted BL positive	MITT
14.4.6	Mean PCF Titer by time	MITT

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16.7 Tables, Figures, and Listings Shells

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