2. SYNOPSIS

Name of Company: Visterra Inc.	**Volume:** (For national authority use only)
Name of Finished Product: Not Applicable	**Page:**
Name of Active Ingredient(s): VIS410	
Title of Study: A Phase 2a Double-blind, Placebo-controlled Study to Assess the Safety and Tolerability of a Single Intravenous Dose of VIS410 in Subjects with Uncomplicated Influenza A Infection	
Protocol Number: VIS410-202	
Study Period:	**Study Phase:** 2a
Date of first patient, first visit: 06 Jan 2017	
Date of last patient, last visit: 27 Oct 2017	
Investigators: A list of Investigators is presented in Appendix 16.1.4.	
Study Center(s): This study was conducted across 58 study centers worldwide.	
Publication(s): Not applicable.	

Objectives:

Primary:

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

Secondary:

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

Exploratory:

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

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VIS410

Study Design:

This was a Phase 2a randomized, double-blind, placebo-controlled study conducted in approximately 150 subjects with uncomplicated influenza. This study included 58 clinical sites worldwide, with 28 sites enrolling at least one subject.

The study was designed to compare an infusion of a single high or low dose of VIS410 against placebo. Subjects were assigned randomly to receive VIS410 at a dose of 2000 mg (low dose) or 4000 mg (high dose) or placebo (0.9% sodium chloride) at a ratio of 1:1:1 using a permuted block randomization method. Eligible subjects received VIS410 2000 mg, VIS410 4000 mg, or placebo administered as a single IV infusion over 2 hours on Day 1 following a pretreatment regimen of diphenhydramine 50 mg per oral (PO) plus either ibuprofen 400 mg PO or acetylsalicylic acid 325 mg PO 60 minutes before infusion.

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

An independent Data Safety Monitoring Board (DSMB) was established to review all available safety data after 30 subjects had completed the Day 5 visit and again after 75 subjects had completed the Day 28 visit. In addition, the DSMB was to convene ad hoc in case of a drug related serious adverse event (SAE) or if the overall relative gastrointestinal (GI) adverse event (AE) rate reached 50% or the rate of moderate GI AEs reached 25%. Once such meeting was held, to allow evaluation of an SAE event (which occurred in a placebo recipient) that was thought to be possibly related to study drug.

Number of Patients (planned and analyzed): Approximately 150 subjects were planned to be included in the study. A total of 150 subjects were randomized to treatment of which 147 subjects completed the trial. All 150 subjects were included in the ITT population and 148 subjects were included in the safety population. A total of 138 subjects were included in the mITT population.

Diagnosis and Criteria for Inclusion:

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

1) Male and female subjects aged ≥18 years and <65 years

2) Women who fulfilled one of the following criteria:

   a) Post-menopausal; either amenorrhea ≥12 months or follicle stimulating hormone >40 mIU/mL as documented in their medical history

   b) Surgically sterile; hysterectomy, bilateral oophorectomy, or tubal ligation

   c) Women of childbearing potential participating in heterosexual sexual relations willing to use adequate contraception from screening until 60 days post-infusion

3) Non-vasectomized (or vasectomized less than 6 months prior to dosing) male subjects who had a female partner of childbearing potential and used an effective birth control method when having heterosexual intercourse, from screening until 60 days post-infusion

4) Test positive for influenza A by Rapid Antigen Test performed with a commercially available test on an adequate nasopharyngeal specimen in accordance with the manufacturer's instructions

5) Presence of at least one respiratory symptom (cough, sore throat, or nasal symptoms) of moderate to severe intensity, or presence of at least one constitutional symptom (myalgia [aches and pains], headache, feverishness, or fatigue) of moderate to severe intensity

6) Onset of symptoms (time when the temperature was first measured as elevated [temperature of ≥100.4°F or ≥38°C], OR the time when the subject experienced at least one respiratory symptom or at least one constitutional symptom) no more than 72 hours before the start of infusion

7) Subject was able and willing to comply with study procedures, as per protocol

8) Subject was able and willing to give voluntary written informed consent

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

1) Use of non-steroidal anti-inflammatory drugs (NSAIDs) or antihistamines within 6 hours of study drug dosing with the exception of those used as part of the pre-treatment regimen

2) History of intolerance or allergic response to monoclonal antibodies and/or pre-treatment medications (diphenhydramine, ibuprofen and acetylsalicylic acid)

3) History of receiving monoclonal antibody products within 3 months prior to enrollment in this study or planned administration during the study period

4) Subjects in whom nasopharyngeal swabbing is not possible

5) Subject weight less than (<) 45 kg

6) Subjects with clinical history that would lead to increased risk of influenza complications including but not limited to clinically significant cardiac disease, moderate to severe asthma, or other moderate to severe chronic obstructive pulmonary disease, metabolic syndrome including moderate to severe diabetes, active tuberculosis, neuromuscular disorders, seizure disorders, or cognitive dysfunction

7) History of chronic GI disease, including bleeding, ulceration, Irritable Bowel Syndrome, systemic mastocytosis, or chronic diarrhea

8) Women who are pregnant, breast-feeding, or considering becoming pregnant

9) Patients with hypoxemia requiring oxygen support

10) Clinical evidence of worsening of any chronic medical condition (temporally associated with the onset of symptoms of influenza) which, in the Investigator's opinion, indicates that such finding(s) could represent complications of influenza

11) Presence of immunocompromised status due to chronic illness, previous organ transplant, or use of immunosuppressive medical therapy including systemic steroids

12) Presence of known Acquired Immune Deficiency Syndrome-defining illness, chronic hepatitis B or hepatitis C

13) Receipt of any dose of antiviral therapy such as, but not limited to, rimantadine, amantadine, peramivir, zanamivir, laninamivir or oseltamivir in the 7 days prior to screening

14) Enrollment in any other investigational drug or device study, any disease or vaccine study within 30 days prior to Day 1 or within 5 half-lives of the investigational compound, whichever is longer

15) Presence of any pre-existing illness that, in the opinion of the Investigator, would place the subject at an unreasonably increased risk through participation in this study

16) Subjects unable to comply with study protocol procedures and study visit schedules for whatever reason

17) Subjects unable to take oral pre-dose medication

18)Known or suspected alcohol or drug abuse, that is, abuse of a level that would compromise the safety or cooperation of the subject in the opinion of the Investigator

19) Subjects on chronic medications where the dose has not been stable for at least 3 months.

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A separate protocol was used for South Africa with an additional exclusion criterion of human immunodeficiency virus (HIV).

Test Product, Dose and Mode of Administration, and Lot Number:
VIS410 2000 mg or VIS410 4000 mg administered as a single IV infusion
Lot Number: B16020009

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Normal saline solution (0.9%)

Duration of Treatment: Single IV infusion on Day 1

Criteria for Evaluation:

Primary Endpoints

- The proportion of subjects with AEs and SAEs following administration of VIS410
- The proportion of subjects with TEAEs including
- Hypersensitivity reaction
- Anaphylactic reaction
- AEs of special interest (AESIs) following dosing

Secondary Endpoints

- The incidence, severity, and duration of signs and symptoms of influenza-like illness as assessed by the FluPRO questionnaire after a single IV dose of VIS410
- Percentage of participants requiring hospitalization for influenza-related complications
- Duration of hospitalization for influenza-related complications
- Percentage of participants with complications of influenza
- Percentage of participants with influenza A relapse/reinfection
- VIS410 PK parameters (C_{max}, time corresponding to maximum serum concentration [t_{max}], area under the concentration-time curve extrapolated to infinity [$AUC_{0-\infty}$], area under the concentration-time curve from time 0 to the last measurable concentration [AUC_{0-last}], elimination half-life ($t_{1/2}$), Volume of distribution [Vd], CL) in serum
- The difference between VIS410 and placebo treatment groups in viral AUC from nasopharyngeal swabs
- The difference between VIS410 and placebo treatment groups in peak viral load (VL) and time to resolution of viral load from nasopharyngeal swabs
- Titer of anti-VIS410 antibody-positive samples

Exploratory Endpoints

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

Statistical Methods:

Efficacy:

Patient Diary - Influenza Patient Reported Outcomes (FluPRO)

FluPRO data were recorded at Baseline (Day 1) and every day thereafter through Day 10. These data were summarized at each visit with counts and percentages by treatment group, including a combined low-dose and high-dose VIS410 group. This analysis was performed using the mITT population.

The domain, component, and total symptom scores were calculated as the mean of the non-missing questions. Low mean scores indicate mild disease. The minimum data requirement for calculating each of the domain symptom scores was: nose 3 of 4 items, throat 2 of 3 items, eyes 2 of 3 items, chest/respiratory 5 of 7 items, GI 3 of 4 items, and body/systemic 8 of 11 items. Total symptom scores were calculated only if the conditions for evaluable data as described above for all individual domains were met.

Time to resolution (in days) for the total symptom score, each domain symptom score (nose, throat, eyes, chest/respiratory, GI, body/systemic) was summarized using n, mean, SD, median, minimum, and maximum. Kaplan-Meier methods were also used to calculate the median time, 25th percentile, and 75th percentile time to resolution. In addition, exploratory analyses of each component symptom score (upper respiratory tract, lower respiratory tract, and generalized) were also performed. These summaries were done by treatment groups and included the combined low-dose and high-dose VIS410 groups in the mITT population. Time to resolution of the total symptom, domain symptom, and component symptom scores were defined as the maximum time to resolution for the individual questions that comprised that total, domain, or component symptom score.

The duration of total symptom score, domain symptom scores, or component symptom scores were primarily defined as the earliest visit day from 2 consecutive means ≤ 1.0; and as an exploratory endpoint as the maximum value of duration across the individual symptoms questions that comprised that total, domain or component symptom score. Kaplan-Meier methods were used to calculate the median time, 25th percentile, and 75th percentile time to resolution.

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

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

The AUC for the total symptom score, 6 domain symptom scores, and 3 component symptom scores was calculated using the linear trapezoidal rule, i.e. $AUCti,-ti+1=1/2*(Si + Si+1)*(ti+1 – ti)$ where Si was the total symptom score at time point ti. All time points from pre-dose to Day 10 were considered.

A sensitivity analysis of the total symptom score, domain symptom scores, and component symptom scores was conducted by repeating the above analysis in the mITT population, excluding subjects who received antiviral therapy for influenza during the first 10 days of the study. Determination of applicable antiviral therapy for influenza was defined before the study was unblinded.

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

Analyses of FluPRO duration of influenza symptoms by total score, domain scores and component scores by time to onset of symptom categories, Baseline HAI titer categories, and by region were also performed.

Patient Diary – Oral Temperature

Subjects were instructed to record an oral temperature every morning and evening, starting on Day 1 and continuing through Day 10. These data were summarized at each visit/time point with continuous statistics n, mean, SD, median, minimum, and maximum. These summaries are presented by treatment group, including the combined low-dose and high dose VIS410 group. This summary was performed using the mITT population. Time to recovery to normal temperature was assessed for each treatment arm and the

combined low dose and high-dose VIS410 group. Normal temperature was defined as 2 consecutive oral temperature of <37.2°C (99°F). Kaplan-Meier methods were used to calculate the median, 25th and 75th percentiles of time to normal temperature. This analysis only included mITT subjects with a Baseline temperature of >38°C.

Complications of Influenza

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

Hospitalizations

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

Influenza A Relapse

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

The initial screening for possible relapse was based on Medical Dictionary for Regulatory Activities (MedDRA) coded AE preferred terms (PTs) of Flu-like symptoms, Flu-like aching, Flu-like illness, or Influenza-like symptoms. The start date for this AE was during the 100-day follow-up period and >7 days after any earlier influenza AE to ensure this was a relapse, rather than a worsening of initial symptoms. No influenza relapse episodes were identified.

Pharmacokinetic Analyses

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) were used to estimate PK parameters in serum and from nasopharyngeal secretions as described below. All calculations used the actual times recorded in the EDC system for dosing and sampling. Individual and mean (± SD) or median concentrations versus time profiles were plotted on both linear and logarithmic scales. Additional plots and PK parameters were generated as appropriate.

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

- C_{max}: maximum serum concentration
- T_{max}: time corresponding to C_{max}
- T_{last}: time of the last measurable concentration
- $AUC_{0-\infty}$: area under the concentration-time curve from time 0 extrapolated to infinity
- $AUC_{\%\ extrap}$: percent extrapolated to AUC0-∞
- AUC_{0-last}: area under the concentration-time curve from time 0 to the last measurable concentration
- $t_{1/2}$: terminal elimination half-life
- CL: total clearance (serum only)

- Vd: volume of distribution (serum only)
- Ratio of nasal: serum AUC in subjects with both values available

Additional PK parameters were determined as appropriate.

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

Serum Pharmacokinetics

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

Nasopharyngeal Secretion Pharmacokinetics

Individual concentrations versus time profiles were plotted on both linear and logarithmic scales in all subjects. Mean (± SD) or median concentrations versus time profiles were plotted on both linear and logarithmic scales for the first 50 subjects enrolled that had the full PK profile collected. Specimens for determination of VIS410 nasopharyngeal secretion concentrations for calculation of the PK parameters listed above were to be collected only from the first 50 subjects enrolled. Summary statistics of nasopharyngeal concentrations (first 50 subjects and in all subjects) and PK parameters (first 50 subjects only) are presented by nominal time of collection including n, mean, geometric mean, SD, CV, median and ranges, as appropriate. Additional analyses and summaries were generated as appropriate.

Correlations between serum PK parameters and nasopharyngeal PK parameters are presented. The ratio of nasal AUC/serum AUC from the Day 3 visit until the last measurement and to infinity were summarized with these statistics.

Anti-influenza A Antibodies

Titer of anti-influenza A antibodies (H1 and H3 strain specific) were 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) were listed as <BLQ and summarized as zero. Values that were <10 (LLOQ) were assessed as 5 and values >10240 (ULOQ) were assessed as 10240.

Nasopharyngeal Viral Load

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) were used to calculate peak VL and the area under the viral load-time curve (VL AUC). The VL at each study visit, proportion of subjects with negative results at each study visit, peak VL, and VL AUC based on quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) and half-maximal tissue culture infective dose ($TCID_{50}$) from nasopharyngeal secretions were 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 were assessed to calculate proportion of subjects with negative results at each study visit. For all other calculated parameters, VL was assessed on all samples in the mITT population collected through the Day 7 visit. In addition, VL and VL AUC for the first 50 subjects was listed through Day 14 (no summary statistics were presented). For missing data on Day 3, Day 5 and Day 7, the analysis was conducted without imputation and with the last observable measurement carried forward (LOCF). For missing data on Day 1, the analysis was conducted by replacing the missing data with the Day 3 observable measurement. Subjects missing both Day 1 and Day 3 virology data were removed from the analysis.

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

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

A sensitivity analysis was also performed that excluded subjects who received antiviral therapy during the study. Determination of applicable antiviral therapy was defined before the study was unblinded. All VL data generated per the analytical plan was listed.

For the influenza A virus subtype H3, virus load data measured by $TCID_{50}$ was determined using both hemagglutination and NP-ELISA as an assay read-out. The sensitivity was higher for NP-ELISA; therefore, all VL parameters were calculated using the data from NP-ELISA only.

Pharmacokinetic and Pharmacodynamic Analyses

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

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

The independent variables (PK exposure parameters) included serum VIS410 AUC and C_{max}. Univariable analyses were conducted to explore the relationship between these independent and dependent variables. Various techniques were used to explore exposure-response relationships. These techniques included 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 were based on the nature of the data, and strengths of relationships identified via graphical evaluation. If appropriate, continuous independent variables were evaluated as such, and also as categorical variables (grouping subjects into exposure categories). Categories based on subject groupings included 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 this CSR, or may be reported separately.

Anti-drug Antibodies

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

Safety:

All AEs were coded using MedDRA version 19.1.

An overall summary of AEs and treatment-emergent AEs (TEAEs) was presented by treatment group, including the combined low-dose and high-dose VIS410, and overall subjects, with subject counts, percentages, and the exact 95% CI for the percentage of subjects with the event. This summary was also presented by region: US, Africa, Rest of the World.

A summary table by treatment group presented the number and percentage of subjects with TEAEs by system organ class (SOC) and SOC/PT. Subjects with multiple TEAEs within an SOC or SOC/PT combination were counted only once for that SOC or SOC/PT combination. This table also presented a summary of subjects with any TEAE.

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

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

A summary table, by treatment group, was presented for the TEAE relationship (reasonable possibility or no reasonable possibility) associated with each SOC and SOC/PT. A subject was counted only once for an SOC or an SOC/PT combination. If a subject experienced multiple events in the same SOC or SOC/PT, the closest relationship to study drug contributed counts to the summary table. A sensitivity analysis of overall TEAEs was conducted excluding subjects from Site 705.

Efficacy Results:

- FluPro total symptom scores were equivalent and generally mild-to-moderate at Baseline. Treatment with VIS410 was associated with a reduction in the FluPRO total symptom score, domain symptom scores, and composite scores by mean percent and mean absolute change from Baseline. In the VIS410 2000 mg treated subjects, the percent decline from Baseline in FluPro total symptom score was significantly greater on Days 3 (p=0.002) through Day 5. Across all VIS410 treated subjects (pooled 2000 and 4000 mg dose) the percent decline from Baseline was significantly greater on Day 4 (p=0.007), thereafter, overall symptom improvement was comparable between treatment arms. In Kaplan-Meier analysis, the time to symptom resolution based on the FluPRO total symptom score (FluPro mean total score of ≤ 1.0) was 2.1 days in all VIS410 treated subjects, versus 2.6 days in placebo treated subjects (p=0.173) in the mITT population. The presence or absence of an HAI (anti-influenza A antibody) titer >1:40 at Baseline did not seem to influence outcome with regard to time to resolution of influenza symptoms.
- The overall rates of influenza complications were low across groups, and no subject was hospitalized due to influenza worsening or complications. In addition, no subject had a relapse of influenza A infection during the study. There was no evidence of enhancement of infectivity of influenza A in VIS410 treated subjects.
- VIS410 was associated with a reduction in viral AUC and duration of viral shedding as measured by $TCID_{50}$, with most subjects showing no culturable virus by Day 5 or 7.
- On Day 3 the percentage of subjects with negative culture was 66.7% in the VIS410 treated group vs. 51.1% in the placebo group (p=0.111). In the subgroup of subjects with positive viral cultures at Baseline, the percentage of subjects with negative culture at Day 3 was 63.2% versus 42.5% among all subjects receiving VIS410 versus subjects receiving placebo, respectively (p=0.053). The Kaplan-Meier estimate of median time to resolution of viral culture positivity by $TCID_{50}$ was 1.9 days for all VIS410 treated subjects, versus 3.6 days for placebo-treated subjects (p=0.028). This same analysis performed in the subgroup of subjects with positive viral cultures at Baseline demonstrated median times to resolution of viral culture positivity of 2.0 versus 3.8 days (p=0.012) for VIS410 versus placebo-treated subjects, respectively. The mean viral load (by $TCID_{50}$) Area Under the Curve (AUC) through Day 7 for all VIS410 recipients was 4.342 (d × log10 $TCID_{50}$/mL) versus 5.399 for placebo recipients (p=0.083) in the mITT population. In an additional subset analysis, among subjects presenting at Baseline with low anti-influenza A antibody titers (Baseline HAI ≤ 40) peak viral load (log10 $TCID_{50}$/mL) and viral AUC by $TCID_{50}$ (d × log10 $TCID_{50}$/mL) were both significantly reduced in recipients of VIS410 versus placebo (p values of 0.027 and 0.009, respectively). VIS410 hastened clearance of viral culture positivity, as assessed in multiple analyses.
- In contrast to the significant differences between placebo-treated and VIS410-treated groups in assessments of viral culture outcomes, no differences were observed between VIS410 and placebo-treated subjects in detection of nasopharyngeal influenza by qRT-PCR. Of note, viral RNA detection by qRT-PCR is extremely sensitive, and may detect non-infectious (neutralized), virus in cellular

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debris and defective virions, in addition to intact virus (while viral culture detects only functional virus).

- VIS410 therapy did not appear to reduce ability to evoke antibody response to influenza A virus as anti-influenza A antibody titers by HAI were similar across groups.
- Following a single IV infusion of VIS410, dose proportional PK was observed (as measured by AUC and C_{max}). The nasal to serum ratio was consistent with expectations for partitioning of a mAb to the nasal cavity, with ~2% VIS410 penetration to the nasal cavity.
- Overall, ADA titers were low with 23% of VIS410 treated subjects having an increase of greater than 4-fold in ADA titer over time. Impact on VIS410 PK was minimal in the presence of ADA, with no impact of ADA status on PK observed in the 28 days following treatment.

Safety Results:

- VIS410 administered as a single IV infusion at a dose of 2000 and 4000 mg following a pre-treatment regimen was generally safe and well tolerated by subjects 18 to 65 years of age, with uncomplicated influenza A infection.
- The incidence of TEAEs was low and similar between VIS410 2000 mg dose and the placebo group. A higher rate of TEAEs was reported with the VIS410 4000 mg dose, mostly clustered in the gastrointestinal SOC.
- TEAEs were mostly mild in intensity and resolved shortly after onset. Only half of the events were considered to be related to the study drug by the Investigator.
- Across all three groups, GI AEs were the most commonly reported TEAEs with a higher rate observed in the VIS410 4000 mg dose. Diarrhea and vomiting were the most common events reported in the VIS410 4000 mg group. The majority of these GI events were mild, did not lead to study discontinuation, and resolved without intervention.
- There were no deaths or discontinuation due to an AE, however, there were 2 SAEs (upper gastrointestinal hemorrhage and cerebrovascular accident) in the placebo group that led to hospitalization.
- No subject reported worsening of influenza symptoms or relapse of infection following VIS410 therapy that may be suggestive of antibody-dependent enhancement (ADE).

In general, laboratory parameters showed minimal changes from Baseline and remained within normal limits during study. No subjects were discontinued from the study for abnormal laboratory values. There were no clinically important trends in vital signs or ECG.

Conclusions:

VIS410 demonstrated trends towards faster resolution of symptoms across total FluPRO scores and most component domain and composite group FluPRO symptom scores. VIS410 demonstrated statistically significant reductions in viral load AUC and duration of viral shedding (by $TCID_{50}$) compared to placebo in subjects with uncomplicated influenza A infection. VIS410 demonstrated linear PK with exposures similar to prior studies.

VIS410 was safe and well tolerated up to a dose of 4000 mg in subjects with uncomplicated influenza. The observed profile was consistent with the known AE profile of VIS410 from previous studies.

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