Clinical trial results:
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

Summary

EudraCT number	2015-004546-26
Trial protocol	BG LV
Global end of trial date	19 October 2018

Results information

Result version number	v1 (current)
This version publication date	29 August 2019
First version publication date	29 August 2019
Summary attachment (see zip file)	VIS410-202 CT Results (VIS410-202 synopsis version 1.0_2018-10-19.pdf)

Trial information

Trial identification

Sponsor protocol code	VIS410-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Visterra, Inc.
Sponsor organisation address	275 2nd Avenue, 4th Floor, Waltham, MA, United States, 02451
Public contact	Kristi Schaefers , Visterra, Inc., 1 617-401-2019, kschaefers@visterra.com
Scientific contact	Kristi Schaefers , Visterra, Inc., 1 617-401-2019, kschaefers@visterra.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2017
Global end of trial reached?	Yes
Global end of trial date	19 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the safety and tolerability of a single intravenous (IV) infusion of 2 dose levels of VIS410 in patients with uncomplicated influenza infection

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) was established to review all available safety data after 30 subjects completed the Day 5 visit and again after 75 subjects completed the Day 28 visit. In addition, following the first DSMB, the DSMB was to convene in case of a drug related serious adverse event (SAE) or if the overall relative GI adverse event (AE) rate reached 50% or the rate of moderate GI AEs reached 25%.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	South Africa: 73
Worldwide total number of subjects	150
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	150
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was initiated in 58 study centers; 28 sites enrolled at least 1 subject.

Pre-assignment

Screening details:

When required, subjects may have been given a pre-screening informed consent in order to perform the Rapid Antigen Test for influenza. Flu-positive subjects were then given a full explanation of the nature of the study and written informed consent was obtained according to local requirements before any study-related assessment was carried out.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

In order to maintain the blind, the site's unblinded pharmacist or properly trained designee prepared the VIS410 or placebo dummy saline infusions according to the instructions in the Pharmacy Manual. The IV infusion bags were covered by an opaque sleeve in the pharmacy to protect the product from light and to maintain the study blind. Blinded site team was given the infusion bag with the opaque sleeve in place ready to be administrated to the subject.

Arms

Are arms mutually exclusive?	Yes
Arm title	VIS410 4000 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	VIS410 4000 mg
Investigational medicinal product code	VIS410
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for infusion was administered as a single IV infusion over 2 hours

Investigational medicinal product name	VIS410 2000 mg
Investigational medicinal product code	VIS410
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for infusion was administered as a single IV infusion over 2 hours

Arm title	VIS410 2000 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	VIS410 2000 mg
Investigational medicinal product code	VIS410
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Solution for infusion was administered as a single IV infusion over 2 hours

Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	VIS410 4000 mg
Investigational medicinal product code	VIS410
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Investigational medicinal product name	VIS410 2000 mg
Investigational medicinal product code	VIS410
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Investigational medicinal product name	Placebo for VIS410
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Number of subjects in period 1	VIS410 4000 mg	VIS410 2000 mg	Placebo
Started	50	50	50
Completed	49	48	50
Not completed	1	2	0
Consent withdrawn by subject	-	1	-
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	VIS410 4000 mg
Reporting group description: -	
Reporting group title	VIS410 2000 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Reporting group values	VIS410 4000 mg	VIS410 2000 mg	Placebo
Number of subjects	50	50	50
Age categorical			
Adults (18-65)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	50	50	50
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	27	29	28
Male	23	21	22

Reporting group values	Total		
Number of subjects	150		
Age categorical			
Adults (18-65)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	150		
From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	84		
Male	66		

Subject analysis sets

Subject analysis set title	Intent to Treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

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

Subject analysis set title	Modified Intent to treat population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat (mITT) population included all subjects who received IV study drug and were confirmed influenza A positive by a molecular test at the central virological laboratory.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all ITT subjects who received IV study drug.

Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Per protocol

Subject analysis set description:

The PK population included all subjects who received IV study drug and had at least 1 PK concentration that could be calculated.

Reporting group values	Intent to Treat population	Modified Intent to treat population	Safety Population
Number of subjects	150	138	148
Age categorical			
Adults (18-65)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	150	138	148
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	Pharmacokinetic Population		
Number of subjects	96		
Age categorical			
Adults (18-65)			
Units: Subjects			

In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	96		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	VIS410 4000 mg
Reporting group description: -	
Reporting group title	VIS410 2000 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Subject analysis set title	Intent to Treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intent-to-treat (ITT) population included all subjects randomized to treatment.	
Subject analysis set title	Modified Intent to treat population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified intent-to-treat (mITT) population included all subjects who received IV study drug and were confirmed influenza A positive by a molecular test at the central virological laboratory.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all ITT subjects who received IV study drug.	
Subject analysis set title	Pharmacokinetic Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PK population included all subjects who received IV study drug and had at least 1 PK concentration that could be calculated.	

Primary: Adverse events and adverse events of interest

End point title	Adverse events and adverse events of interest[1]

End point description:

- 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

End point type	Primary

End point timeframe:

3.3 months (100 ± 7 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: An overall summary of AEs, TEAEs, and adverse events of interest 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.

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Safety Population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	49	49	50	148
Units: Number of patients				
Subjects with any TEAE	27	17	12	58
Subjects With Any Treatment-Related TEAE	15	7	6	28
Subjects with any SAEs	0	0	2	2
Subjects With Any Treatment-Related SAEs	0	0	1	1
Subjects With Any TEAEs of Special Interest	17	8	6	31
Hypersensitivity reaction	0	0	0	0
Anaphylactic reaction	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: FluPRO Questionnaire Total Symptom Score

End point title	FluPRO Questionnaire Total Symptom Score

End point description:

FluPRO data were recorded by subjects at Baseline (Day 1), then daily thereafter through Day 10. These data were summarized at each visit 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 for an individual were calculated as the mean of the questions that were non-missing. 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 of missing data for all domains were met.

End point type	Secondary

End point timeframe:

10 days

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	46	44	48	138[2]
Units: Total Symptoms Score				
arithmetic mean (standard deviation)				
Percent change from baseline to Day 2	-26.12 (± 27)	-29.98 (± 29.55)	-19.53 (± 26.51)	0 (± 0)
Percent change from baseline to Day 3	-38.65 (± 28.78)	-49.37 (± 29.62)	-33.63 (± 23.6)	0 (± 0)
Percent change from baseline to Day 4	-53.46 (± 26.16)	-59.08 (± 31.12)	-44.55 (± 28.2)	0 (± 0)
Percent change from baseline to Day 5	-60.85 (± 25.52)	-64.61 (± 29.91)	-56.75 (± 24.31)	0 (± 0)

Percent change from baseline to Day 6	-69.31 (± 20.90)	-66.8 (± 33.42)	-64.01 (± 23.35)	0 (± 0)
Percent change from baseline to Day 7	-74.03 (± 19.31)	-70.76 (± 31.18)	-71.51 (± 20.61)	0 (± 0)
Percent change from baseline to Day 8	-77.98 (± 20.76)	-76.03 (± 25.53)	-76.16 (± 21.01)	0 (± 0)
Percent change from baseline to Day 9	-80.05 (± 19.78)	-78.48 (± 25.95)	-79.27 (± 22.91)	0 (± 0)
Percent change from baseline to Day 10	-82.30 (± 20.07)	-81.38 (± 20.43)	-84.35 (± 17.52)	0 (± 0)

Notes:

[2] - Combined data not summarized

Statistical analyses

Statistical analysis title	Pt Diary - Influenza Pt Reported Outcomes (FluPRO)

Statistical analysis description:

FluPRO data were recorded by subjects at Baseline (Day 1), then daily thereafter through Day 10. These data were summarized at each visit 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 for an individual were calculated as the mean of the questions that were non-missing. Low mean scores indicate mild disease. The minimum data requirement for calculating each of t

Comparison groups	VIS410 2000 mg v VIS410 4000 mg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.173
Method	Logrank

Secondary: Hospitalization for influenza-related complications

End point title	Hospitalization for influenza-related complications

End point description:

- Percentage of participants requiring hospitalization for influenza-related complications

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	46	44	48	138
Units: Percentage of participants requiring h				
number (not applicable)				
Hospitalized for influenzas-related complications	0	0	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Complications of influenza

End point title	Complications of influenza

End point description:

- Percentage of participants with complications of influenza

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	46	44	48	138
Units: Percentage of participants with compli				
number (not applicable)				
influenzas-related complications	1	3	3	7

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with influenza A relapse/reinfection

End point title	Percentage of participants with influenza A relapse/reinfection

End point description:

- Percentage of participants with influenza A relapse/reinfection

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	46	44	48	138
Units: Percentage of participants with influenz				
number (not applicable)				
influenza A relapse	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: VIS410 PK parameters

End point title	VIS410 PK parameters[3]

End point description:

- VIS410 PK parameters (Cmax, time corresponding to maximum serum concentration [tmax], area under the concentration-time curve extrapolated to infinity [AUC0-∞], area under the concentration-time curve from time 0 to the last measurable concentration [AUC0-last], elimination half-life (t1/2), Volume of distribution [Vd]), and clearance (CL) in serum

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) were used to estimate PK parameters.

End point values	VIS410 4000 mg	VIS410 2000 mg	Modified Intent to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	47	49	96[4]	
Units: Cmax, Tmax, AUC				
arithmetic mean (standard deviation)				
AUC 0 to infinity	9157.319 (± 3209.0221)	5592 (± 1544.29)	0 (± 0)	
AUC 0 to last	24.722 (± 3250)	5624 (± 1619)	0 (± 0)	
Cmax	1066 (± 313)	729 (± 574)	0 (± 0)	
T ½	10.42 (± 2.35)	10.645 (± 3.35)	0 (± 0)	
Clearance	499.8 (± 211.659)	329.2 (± 124.8)	0 (± 0)	
Tmax	.210 (± .4873)	0.428 (± 1.28)	0 (± 0)	
Volume of distribution	7187 (± 2897)	5730 (± 1843)	0 (± 0)	

Notes:

[4] - Totalk PK not calculated

Statistical analyses

No statistical analyses for this end point

Secondary: Viral load AUC

End point title	Viral load AUC

End point description:

- The difference between VIS410 and placebo treatment groups in viral AUC from nasopharyngeal swabs

End point type	Secondary

End point timeframe:

Day 7

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	46	44	48	138
Units: viral AUC from nasopharyngeal swabs				
arithmetic mean (standard deviation)				
Viral load AUC	25.352 (± 7.4381)	25.856 (± 8.2532)	26.535 (± 7.8894)	25.914 (± 7.8602)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak viral load

End point title	Peak viral load

End point description:

- The difference between VIS410 and placebo treatment groups in peak VL from nasopharyngeal swabs

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	50	50	50	90[5]
Units: Peak VL from nasopharyngeal swabs				
arithmetic mean (standard deviation)				
Peak viral load	6.686 (± 1.1195)	6.26 (± 1.0187)	6.713 (± 1.4354)	6.657 (± 1.0658)

Notes:

[5] - Total VIS410 group only (no data for placebo)

Statistical analyses

Statistical analysis title	Viral Load

Statistical analysis description:

Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) were used to calculate peak VL and 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 qRT-PCR and half-maximal tissue culture infective dose (TCID50) from nasopharyngeal secretions were summarized with n, mean, SD, geometric mean, CV, minimum and maximum values in the mITT population overal

Comparison groups	VIS410 4000 mg v VIS410 2000 mg v Placebo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.795
Method	Phoenix WinNonlin

Secondary: Resolution of viral load

End point title	Resolution of viral load

End point description:

- The difference between VIS410 and placebo treatment groups in time to resolution of VL from nasopharyngeal swabs

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	46	44	48	90
Units: time to resolution of VL from swabs				
arithmetic mean (confidence interval 95%)				
Resolution of viral load (days)	2.100 (1.79 to 3.77)	1.870 (1.83 to 1.99)	3.790 (1.83 to 3.900)	1.9 (1.84 to 2.10)

Statistical analyses

No statistical analyses for this end point

Secondary: Antidrug Antibodies

End point title	Antidrug Antibodies

End point description:

- Titer of anti-VIS410 antibody-positive samples

End point type	Secondary

End point timeframe:

100 days

End point values	VIS410 4000 mg	VIS410 2000 mg	Placebo	Modified Intent to treat population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	49[6]	47[7]	47[8]	96[9]
Units: Anti-VIS410 antibody-positive samples				
arithmetic mean (standard deviation)				
Baseline Positive	6 (± 12.2)	4 (± 8.5)	4 (± 8.5)	10 (± 10.4)
Baseline Negative	43 (± 87.8)	43 (± 91.5)	43 (± 91.5)	86 (± 89.6)
Day 100 Positive	20 (± 40.8)	22 (± 47.8)	6 (± 12)	42 (± 44.2)
Day 100 Negative	29 (± 59.2)	24 (± 52.2)	44 (± 88)	53 (± 55.8)

Notes:

[6] - Values reported are n and %

[7] - Values reported are n and %

[8] - Values reported are n and %

[9] - Values reported are n and % . Includes only pts receiving VIS410

Statistical analyses

Statistical analysis title	Antidrug Antibodies

Statistical analysis description:

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

Comparison groups	VIS410 4000 mg v VIS410 2000 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Phoenix WinNonlin
Parameter estimate	Phoenix Win non-lin

Secondary: PK data from nasopharyngeal swab

End point title	PK data from nasopharyngeal swab[10]

End point description:

- PK parameters (Cmax, tmax, AUC0-∞, AUC0-last, t1/2, AUC ratio for nasopharyngeal: serum) of VIS410 from nasopharyngeal secretions

End point type	Secondary

End point timeframe:

3.3 Months (100 ± 7 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Standard non-compartmental approaches using Phoenix WinNonlin (Pharsight Corporation, Princeton, NJ, USA; Version 7.0 or higher) were used to estimate PK parameters.

End point values	VIS410 4000 mg	VIS410 2000 mg	Modified Intent to treat population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	47	49	96[11]	
Units: PK parameters				
arithmetic mean (standard deviation)				
AUC 0 to infinity	288.575 (± 254.0967)	186.133 (± 197.7161)	0 (± 0)	
AUC 0 to last	290.009 (± 235.2349)	144.878 (± 176.0992)	0 (± 0)	
Cmax	30.942 (± 22.3197)	15.157 (± 15.8274)	0 (± 0)	
T ½	9.97 (± 3.033)	10.201 (± 3.5959)	0 (± 0)	
Nasal to serum ratio Day 3 to infinity	3.77 (± 2.8818)	2.761 (± 2.2756)	0 (± 0)	
Tmax	3.445 (± 1.9168)	3.212 (± 3.0468)	0 (± 0)	

Notes:

[11] - Data not collected for combined groups

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalization for influenza related complications

End point title	Duration of Hospitalization for influenza related complications

End point description:

End point type	Secondary

End point timeframe:

Overall trial

End point values	Modified Intent to treat population			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: day				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3.3 Months (100 ± 7 days)

Adverse event reporting additional description:

- 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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	VIS410 4000 mg

Reporting group description:

All patients who received treatment

Reporting group title	VIS410 2000 mg

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	VIS410 4000 mg	VIS410 2000 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	2 / 50 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebrovascular accident	Additional description: No action was taken with regard to the study drug because of this event.		
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage	Additional description: No action was taken with regard to the study drug because of these events.		
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	VIS410 4000 mg	VIS410 2000 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)	49 / 49 (100.00%)	48 / 50 (96.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	2 / 50 (4.00%)
occurrences (all)	3	2	2
General disorders and administration site conditions			
Number of Subjects with any TEAE			
subjects affected / exposed	27 / 49 (55.10%)	17 / 49 (34.69%)	12 / 50 (24.00%)
occurrences (all)	27	17	12
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	13 / 49 (26.53%)	8 / 49 (16.33%)	6 / 50 (12.00%)
occurrences (all)	13	8	6
Vomiting			
subjects affected / exposed	4 / 49 (8.16%)	0 / 49 (0.00%)	1 / 50 (2.00%)
occurrences (all)	4	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2016	All countries- Modified safety assessments, clinical doses, and pretreatment regimens
12 October 2016	South Africa specific- Inclusion of HIV testing at Baseline
15 November 2016	Latvia specific- Revised to address VHP GNA comments of 7 November 2016
14 March 2017	South Africa specific- Modification of HIV exclusion criteria #12

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 June 2017	The Study was put on halt for one day and a half, the timeframe DSMB needed to meet with urgency and decide if it was safe to continue with the Study after evaluating SAE for patient 80811. Unfortunately, patient 80716 was being randomized at the time of the halt, and it was decided not to dose this patient since it couldn't be done without DSMB meeting outcome. DSMB concluded that the study recruitment could be resumed, and study could continue as per study protocol. However, it was late for patient 80716 that couldn't be dosed as it was outside the protocol allowed window.	29 June 2017

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In this study, VIS410 therapy did not appear to reduce the ability to elaborate an antibody response to influenza A virus as anti-influenza A antibody titers were similar to that of the placebo group.

Notes: