Clinical trial results:
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

Summary

EudraCT number	2016-004009-15
Trial protocol	ES BG EE LV BE
Global end of trial date	22 November 2018

Results information

Result version number	v1 (current)
This version publication date	13 November 2020
First version publication date	13 November 2020

Trial information

Trial identification

Sponsor protocol code	VIS410-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03040141
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Visterra, Inc.
Sponsor organisation address	275 2nd Ave, Waltham, United States, 02451
Public contact	Kristi Schaefers, Visterra, Inc., 1 6174981070, clinicaltrials@visterrainc.com
Scientific contact	Kristi Schaefers, Visterra, Inc., 1 6174981070, clinicaltrials@visterrainc.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	02 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 November 2018
Global end of trial reached?	Yes
Global end of trial date	22 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of 2 dose levels of VIS410 + oseltamivir on clinical outcomes as assessed by comparison of clinical status ordinal scale Day 7 scores between treatment groups, and between all VIS410 dose groups versus placebo.

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) was established to review all available safety data after 30 subjects and again after approximately 70 subjects completed the Day 14 visit. Additional DSMB reviews could have occurred throughout the trial as deemed necessary by the DSMB or Sponsor to ensure subject safety and well being.

Background therapy:

Administration of concomitant medications was reported in the appropriate section of the EDC system along with dates of administration and reasons for use. Subjects were allowed to receive up to 6 doses of an approved anti-influenza therapy (i.e., oral oseltamivir, inhaled zanamivir, or oral ribavirin) within the 96 hours between the onset of symptoms and VIS410/placebo dosing. These 6 doses were to be counted toward the overall 20 doses of oseltamivir which the subject could receive before and during the study. Subjects were not allowed to receive monoclonal antibody products within 3 months prior to VIS410/placebo dosing.

Evidence for comparator:

Placebo-controlled, double-blind study

Actual start date of recruitment	02 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Estonia: 9
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Belarus: 1
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Serbia: 14
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Singapore: 1

Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	89
EEA total number of subjects	42

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	49
From 65 to 84 years	33
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

This study was initiated in 115 study centers; 34 sites enrolled at least 1 subject.

Pre-assignment

Screening details:

Samples from prospective subjects admitted to the hospital within 5 days of onset of initial symptoms who required supplemental oxygen were evaluated via a diagnostic assay to confirm influenza A infection. Flu-positive subjects were then given a full explanation of the nature of the study and written informed consent was obtained.

Period 1

Period 1 title	Treatment Period & Follow up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The study was blinded using placebo infusion to prevent bias in the assessment of effect. The investigative site personnel, the Sponsor, and their representatives involved in the monitoring or conduct of the study, and the subjects were blinded to the study drug codes. In addition, the infusion bag was covered with an opaque sleeve in the pharmacy to maintain the study blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	VIS410 4000

Arm description: -

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

Dosage and administration details:

VIS410 4000 mg was administered IV over 2 hours as single 200-mL infusions followed by a 25-mL (or volume equivalent to length of IV line) saline flush to ensure all the product was administered.

Arm title	VIS410 2000

Arm description: -

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

Dosage and administration details:

VIS410 2000 mg was administered IV over 2 hours as single 200-mL infusions followed by a 25-mL (or volume equivalent to length of IV line) saline flush to ensure all the product was administered.

Arm title	Placebo

Arm description: -

Arm type	Placebo

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

Dosage and administration details:

Placebo was administered IV over 2 hours as single 200-mL infusions followed by a 25-mL (or volume equivalent to length of IV line) saline flush to ensure all the product was administered.

Number of subjects in period 1	VIS410 4000	VIS410 2000	Placebo
Started	29	30	30
Completed	25	24	24
Not completed	4	6	6
Adverse event, serious fatal	1	2	3
Consent withdrawn by subject	3	1	1
subject did not receive study drug	-	2	2
Subject discharged	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period & Follow up

Reporting group description: -

Reporting group values	Treatment Period & Follow up	Total	
Number of subjects	89	89	
Age categorical Units: Subjects			
Adults (18-64 years)	49	49	
From 65-84 years	33	33	
85 years and over	7	7	
Age continuous Units: years			
arithmetic mean	61.2		
standard deviation	± 18.91	-	
Gender categorical Units: Subjects			
Female	45	45	
Male	44	44	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) population included all subjects randomized to treatment and are grouped according to the treatment assigned

Subject analysis set title	MITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified ITT (MITT) population included all subjects who received IV study drug and were confirmed influenza A positive by qRT-PCR in central lab analysis of pre-dose Day 1 and/or post-dose Day 1. Subjects were grouped according to the randomly assigned treatment. All efficacy analyses including the primary efficacy analyses were performed in the MITT population.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all ITT subjects who received IV study drug. Subjects were grouped according to the actual treatment received.

Reporting group values	ITT	MITT	Safety
Number of subjects	88	85	88
Age categorical Units: Subjects			
Adults (18-64 years)	49	46	48
From 65-84 years	33	32	33
85 years and over	7	7	7

Age continuous Units: years			
arithmetic mean	61.2	61.2	61.2
standard deviation	± 18.75	± 18.91	± 18.86
Gender categorical Units: Subjects			
Female	45	44	45
Male	44	41	43

End points

End points reporting groups

Reporting group title	VIS410 4000
Reporting group description: -	
Reporting group title	VIS410 2000
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) population included all subjects randomized to treatment and are grouped according to the treatment assigned	
Subject analysis set title	MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The modified ITT (MITT) population included all subjects who received IV study drug and were confirmed influenza A positive by qRT-PCR in central lab analysis of pre-dose Day 1 and/or post-dose Day 1. Subjects were grouped according to the randomly assigned treatment. All efficacy analyses including the primary efficacy analyses were performed in the MITT population.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all ITT subjects who received IV study drug. Subjects were grouped according to the actual treatment received.	

Primary: Summary of Clinical Status Ordinal Scale

End point title	Summary of Clinical Status Ordinal Scale
End point description:	
For use in overall summary statistical presentations, frequencies of ordinal scores at each visit were generated and evaluated by proportional odds ratio analysis, as implemented by logistic regression, including a test of the proportional odds assumption and generation of estimates of odds ratios. For this analysis, the reference response category was best (1=Discharge with full resumption of normal activities) to worst (7=Death).	
End point type	Primary
End point timeframe:	
Day 7	

End point values	VIS410 4000	VIS410 2000	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: Persons				
Death	1	1	1	
ICU Stay with Mechanical Ventilation	1	2	1	
ICU Stay without Mechanical Ventilation	2	0	0	
Non-ICU hospitalization with Supplemental O2	5	5	3	
Non-ICU hospitalization without Supplemental O2	12	8	10	

Discharge/partial resumption of normal activities	7	5	11	
Discharge/full resumption of normal activities	1	7	2	

Statistical analyses

Statistical analysis title	proportional odds ratio analysis
Comparison groups	VIS410 4000 v VIS410 2000 v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.435 [1]
Method	Regression, Logistic

Notes:

[1] - P-values and Odds Ratios reflect comparisons to placebo evaluated by proportional odds ratio analysis, as implemented by logistic
regression, including a test of the proportional odds assumption

Secondary: Time to Cessation of Oxygen Support

End point title	Time to Cessation of Oxygen Support

End point description:

End point type	Secondary

End point timeframe:

Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	18	15	15	85
Units: hours				
median (inter-quartile range (Q1-Q3))	92.5 (45.5 to 138.7)	101.3 (26.9 to 114.6)	79.0 (41.7 to 103.2)	92 (26.9 to 138.7)

Statistical analyses

Statistical analysis title	Wald Chi-square statistic
Comparison groups	VIS410 4000 v VIS410 2000 v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.902
Method	Chi-squared corrected

Notes:
[2] - Wald Chi-square statistic

Secondary: Time to First Room Air Oxygen > 92%

End point title	Time to First Room Air Oxygen > 92%

End point description:

End point type	Secondary

End point timeframe:
Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	22	25	85
Units: hours				
median (inter-quartile range (Q1-Q3))	88.0 (24.1 to 156.4)	74.2 (35.0 to 100.2)	74.2 (43.5 to 120.6)	80 (24.1 to 156.4)

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	VIS410 2000 v VIS410 4000 v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8679
Method	Logrank

Secondary: Time to First Room Air Oxygen > 94%

End point title	Time to First Room Air Oxygen > 94%

End point description:

End point type	Secondary

End point timeframe:
Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	27	28	85
Units: hours				
median (inter-quartile range (Q1-Q3))	90.7 (37.0 to 162.6)	101.3 (38.9 to 124.7)	86.3 (50.5 to 120.6)	90 (37 to 162.6)

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	VIS410 2000 v Placebo v VIS410 4000
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8834
Method	Logrank

Secondary: Time to Clinical Response (Resolution of Vital Signs)

End point title	Time to Clinical Response (Resolution of Vital Signs)

End point description:

End point type	Secondary

End point timeframe:

Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	28	28	85
Units: hours				
median (inter-quartile range (Q1-Q3))	2.6 (2.2 to 21.9)	2.6 (2.2 to 24.0)	2.8 (2.2 to 44.2)	2.6 (2.2 to 44.2)

Statistical analyses

Statistical analysis title	Cox proportional hazards model Wald Chi-Square
Comparison groups	VIS410 4000 v VIS410 2000 v Placebo

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.157
Method	Chi-squared

Secondary: Time to Complete Clinical Response (normalization of 5 of 5 vital signs)

End point title	Time to Complete Clinical Response (normalization of 5 of 5 vital signs)

End point description:

End point type	Secondary

End point timeframe:

Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	28	28	0[3]
Units: hours				
median (inter-quartile range (Q1-Q3))	103.0 (45.4 to 170.6)	114.6 (47.5 to 166.1)	99.8 (63.0 to 168.5)	(to)

Notes:

[3] - Values for the total MITT group were not calculated

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	VIS410 4000 v VIS410 2000 v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5487
Method	Logrank

Secondary: FLU-PRO Total Symptom Score

End point title	FLU-PRO Total Symptom Score

End point description:

End point type	Secondary

End point timeframe:

Day 1- Day 14

End point values	VIS410 4000	VIS410 2000	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: unit(s)				
arithmetic mean (standard deviation)				
Baseline/Day 1	1.27 (± 0.605)	1.22 (± 0.827)	1.37 (± 0.641)	
Day 2	0.75 (± 0.494)	0.77 (± 0.552)	0.96 (± 0.658)	
Day 3	0.64 (± 0.369)	0.63 (± 0.528)	0.69 (± 0.499)	
Day 4	0.44 (± 0.264)	0.41 (± 0.480)	0.46 (± 0.291)	
Day 5	0.38 (± 0.234)	0.36 (± 0.448)	0.44 (± 0.427)	
Day 6	0.35 (± 0.239)	0.32 (± 0.313)	0.42 (± 0.399)	
Day 7	0.30 (± 0.268)	0.35 (± 0.390)	0.39 (± 0.441)	
Day 8	0.25 (± 0.198)	0.27 (± 0.292)	0.37 (± 0.416)	
Day 9	0.23 (± 0.172)	0.27 (± 0.276)	0.24 (± 0.324)	
Day 10	0.37 (± 0.514)	0.26 (± 0.287)	0.31 (± 0.402)	
Day 11	0.38 (± 0.639)	0.26 (± 0.250)	0.29 (± 0.433)	
Day 12	0.34 (± 0.602)	0.22 (± 0.262)	0.21 (± 0.275)	
Day 13	0.36 (± 0.658)	0.19 (± 0.233)	0.23 (± 0.307)	
Day 14	0.19 (± 0.193)	0.17 (± 0.182)	0.17 (± 0.228)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	VIS410 4000 v Placebo v VIS410 2000
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05 [4]
Method	ANOVA

Notes:

[4] - No statistically significant differences were noted between the VIS410 groups and placebo or between the VIS410 treatment groups

Secondary: Improvement in signs and symptoms: VAS

End point title	Improvement in signs and symptoms: VAS

End point description:

End point type	Secondary

End point timeframe:

Day 1- Day 14

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	29	28	28	0[5]
Units: score				
arithmetic mean (standard deviation)				
Day 1	3.1 (± 1.89)	2.4 (± 1.97)	2.5 (± 1.90)	()
Day 2	3.6 (± 2.06)	3.9 (± 2.52)	3.4 (± 2.46)	()
Day 3	4.3 (± 2.04)	4.5 (± 2.69)	4.6 (± 2.53)	()
Day 4	4.9 (± 2.06)	5.4 (± 2.81)	5.5 (± 2.37)	()
Day 5	6.0 (± 2.18)	5.7 (± 2.89)	5.6 (± 1.84)	()
Day 6	6.3 (± 2.14)	5.7 (± 3.56)	6.2 (± 2.35)	()
Day 7	7.1 (± 1.78)	6.7 (± 2.93)	6.6 (± 2.36)	()
Day 8	7.2 (± 1.73)	7.0 (± 2.91)	6.9 (± 2.64)	()
Day 9	7.0 (± 1.63)	6.5 (± 2.83)	6.9 (± 2.33)	()
Day 10	6.7 (± 2.33)	6.5 (± 2.67)	6.5 (± 2.50)	()
Day 11	7.1 (± 1.76)	6.6 (± 2.30)	7.1 (± 2.66)	()
Day 12	7.5 (± 1.63)	7.0 (± 2.28)	6.3 (± 2.40)	()
Day 13	6.8 (± 2.17)	7.7 (± 1.51)	7.1 (± 2.59)	()
Day 14	7.9 (± 2.18)	7.3 (± 2.16)	7.2 (± 2.99)	()

Notes:

[5] - Values for the total MITT population were not calculated

Statistical analyses

Statistical analysis title	ANOVA using ranked values
Comparison groups	VIS410 4000 v Placebo v VIS410 2000
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.05
Method	ANOVA

Notes:

[6] - no treatment effect differences in VAS scores were detected

Secondary: Ventilator Support

End point title	Ventilator Support

End point description:

End point type	Secondary

End point timeframe:

Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	MITT
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	3	1	85
Units: Days				
median (inter-quartile range (Q1-Q3))	2.5 (2.0 to 10)	10 (4 to 10)	3 (3 to 3)	5 (2 to 10)

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization: Total Number of Days in Hospital/ICU

End point title	Healthcare Resource Utilization: Total Number of Days in Hospital/ICU

End point description:

End point type	Secondary

End point timeframe:

Anytime

End point values	VIS410 4000	VIS410 2000	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: Days				
arithmetic mean (standard deviation)	11.4 (± 8.60)	9.6 (± 7.02)	9.6 (± 6.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Virologic response: changes in nasopharyngeal influenza titers by culture

End point title	Virologic response: changes in nasopharyngeal influenza titers by culture

End point description:

End point type	Secondary

End point timeframe:

Up to Day 7

End point values	VIS410 4000	VIS410 2000	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	28	
Units: Number of negative subjects				
Day 1 predose	7	6	11	
Day 1 postdose	7	6	9	
Day 3	23	24	19	
Day 5	25	26	28	
Day 7	28	27	27	

Statistical analyses

Statistical analysis title	logistic regression

Statistical analysis description:

For use in overall summary statistical presentations, frequencies of ordinal scores at each visit were generated and evaluated by proportional odds ratio analysis, as implemented by logistic regression, including a test of the proportional odds assumption and generation of estimates of odds ratios. For this analysis, the reference response category was best (1=Discharge with full resumption of normal activities) to worst (7=Death).

Comparison groups	VIS410 4000 v VIS410 2000 v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.05
Method	proportional odds ratio
Parameter estimate	Mean difference (final values)

Notes:

[7] - Results were not statistically significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 56

Adverse event reporting additional description:

"Non serious" adverse events includes both serious and nonserious events occurring greater than or equal to 5% of subjects. All serious adverse events are reported. Six deaths were reported in the study (Table 14.3.1.10); 3 subjects who received VIS410 (1 who received 4000 mg and 2 who received received 2000mg); None were related to study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

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

Reporting group description: -

Serious adverse events	VIS410 4000	VIS410 2000	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	4 / 29 (13.79%)	6 / 30 (20.00%)
number of deaths (all causes)	1	2	3
number of deaths resulting from adverse events	1	2	3
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
cardiac failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome	Additional description: Single subject; concurrent with Pneumonia and Sepsis		
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic encephalopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 29 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Failure to thrive			
subjects affected / exposed	1 / 29 (3.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	VIS410 4000	VIS410 2000	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 29 (55.17%)	17 / 29 (58.62%)	10 / 30 (33.33%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 29 (6.90%)	2 / 29 (6.90%)	3 / 30 (10.00%)
occurrences (all)	2	2	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 29 (17.24%)	4 / 29 (13.79%)	0 / 30 (0.00%)
occurrences (all)	5	4	0
Dyspepsia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	4 / 29 (13.79%)	2 / 29 (6.90%)	1 / 30 (3.33%)
occurrences (all)	4	2	1
Vomiting			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	2
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 29 (3.45%)	3 / 29 (10.34%)	2 / 30 (6.67%)
occurrences (all)	1	3	2
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 29 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 29 (10.34%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 29 (0.00%)	3 / 29 (10.34%)	1 / 30 (3.33%)
occurrences (all)	0	3	1
Hypokalaemia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Hypomagnesaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2017	Sample size adjustment; reduced to 120 subjects.
19 April 2018	• Reduction in number of sites. • Decreasing sample size from 390 to 120 subjects to enable completion in 2 influenza seasons; therefore, second DSMB review not required. • Clarification added to ensure all study product administered. Some sites used infusion lines with hold-up volumes of greater than 25 mL. • Utility of ordinal scale observed in prior trials of this size. • Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) added to complete the assays being performed. • Primary objective changed. • Time to cessation of oxygen support changed from primary endpoint to secondary. Some subjects may be on oxygen with SpO2 > 92% at baseline. • Added ordinal scale parameters to be assessed. • Removed interim analysis as sample size decreased to 120 subjects; final analysis to be performed upon completion of enrollment. • Statistical analysis changed due to the decrease in sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported