Clinical trial results:
A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, and Being Treated With Orkambi

Summary

EudraCT number	2015-004841-13
Trial protocol	IE GB FR CZ
Global end of trial date	12 October 2017

Results information

Result version number	v1
This version publication date	29 April 2018
First version publication date	29 April 2018

Trial information

Trial identification

Sponsor protocol code	VX15-371-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02709109
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 6173416777, medical_info@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 6173416777, medical_info@vrtx.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2017
Global end of trial reached?	Yes
Global end of trial date	12 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of treatment with VX-371 in hypertonic saline (HS) compared to HS alone in subjects with cystic fibrosis (CF) who are greater than or equal to (>=) 12 years of age, homozygous for the F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation, and being treated with Orkambi.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2016
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	United Kingdom: 30
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	United States: 92
Worldwide total number of subjects	142
EEA total number of subjects	50

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)	55

Adults (18-64 years)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were randomized to 1 of 4 treatment sequences, each of which included 2 treatment periods. Treatment periods were separated by 28 day washout period.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1 (VX-371 + HS, Then HS): VX-371 + HS

Arm description:

Subjects received VX-371 in combination with 3 milliliter (mL) 4.2% hypertonic saline (HS) in treatment period 1 followed by HS alone in treatment period 2.

Arm type	Experimental
Investigational medicinal product name	VX-371
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

VX-371 administered twice daily for 28 days in treatment period 1.

Investigational medicinal product name	Hypertonic saline (HS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

HS administered twice daily for 28 days in treatment period 1.

Arm title	Sequence 2 (HS, Then VX-371 + HS): HS

Arm description:

Subjects received 3 mL 4.2% HS in treatment period 1 followed by VX-371 in combination with 3 mL 4.2% HS in treatment period 2.

Arm type	Experimental
Investigational medicinal product name	Hypertonic saline (HS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

HS administered twice daily for 28 days in treatment period 1.

Arm title	Sequence 3 (VX-371 + placebo, then placebo): VX-371 + placebo

Arm description:	
Subjects received VX-371 in combination with placebo (0.17% saline) in treatment period 1 followed by placebo (0.17% saline) alone in treatment period 2.	
Arm type	Experimental
Investigational medicinal product name	VX-371
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
VX-371 administered twice daily for 28 days in treatment period 1.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Placebo (0.17% saline) administered twice daily for 28 days in treatment period 1.	
Arm title	Sequence 4 (Placebo, Then VX-371 + placebo): Placebo
Arm description:	
Subjects received placebo (0.17% saline) in treatment period 1 followed by VX-371 in combination with placebo (0.17% saline) in treatment period 2.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Placebo (0.17% saline) administered twice daily for 28 days in treatment period 1.	

Number of subjects in period 1	Sequence 1 (VX-371 + HS, Then HS): VX-371 + HS	Sequence 2 (HS, Then VX-371 + HS): HS	Sequence 3 (VX-371 + placebo, then placebo): VX-371 + placebo
Started	49	47	22
Completed	45	42	21
Not completed	4	5	1
Subject refused further dosing (not due to AE)	-	2	-
Adverse event	3	3	1
Noncompliance with study drug	1	-	-

Number of subjects in period 1	Sequence 4 (Placebo, Then VX-371 + placebo): Placebo
Started	24
Completed	24
Not completed	0

Subject refused further dosing (not due to AE)	-
Adverse event	-
Noncompliance with study drug	-

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1 (VX-371 + HS, Then HS): HS

Arm description:

Subjects received VX-371 in combination with 3 mL 4.2% HS in treatment period 1 followed by HS alone in treatment period 2.

Arm type	Experimental
Investigational medicinal product name	Hypertonic saline (HS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

HS administered twice daily for 28 days in treatment period 2.

Arm title	Sequence 2 (HS, Then VX-371 + HS): VX-371 + HS

Arm description:

Subjects received 3 mL 4.2% HS in treatment period 1 followed by VX-371 in combination with 3 mL 4.2% HS in treatment period 2.

Arm type	Experimental
Investigational medicinal product name	Hypertonic saline (HS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

HS administered twice daily for 28 days in treatment period 2.

Investigational medicinal product name	VX-371
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

VX-371 administered twice daily for 28 days in treatment period 2.

Arm title	Sequence 3 (VX-371 + placebo, then placebo): Placebo

Arm description:	
Subjects received VX-371 in combination with placebo (0.17% saline) in treatment period 1 followed by placebo (0.17% saline) alone in treatment period 2.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Placebo (0.17% saline) administered twice daily for 28 days in treatment period 2.	
Arm title	Sequence 4 (Placebo, Then VX-371 + placebo): VX-371 + placebo
Arm description:	
Subjects received placebo (0.17% saline) in treatment period 1 followed by VX-371 in combination with placebo (0.17% saline) in treatment period 2.	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Placebo (0.17% saline) administered twice daily for 28 days in treatment period 2.	
Investigational medicinal product name	VX-371
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
VX-371 administered twice daily for 28 days in treatment period 2.	

Number of subjects in period 2[1]	Sequence 1 (VX-371 + HS, Then HS): HS	Sequence 2 (HS, Then VX-371 + HS): VX-371 + HS	Sequence 3 (VX-371 + placebo, then placebo): Placebo
Started	43	40	18
Completed	41	36	15
Not completed	2	4	3
Other noncompliance	-	1	1
Requires prohibited medication	-	-	1
Adverse event	2	3	-
Unspecified	-	-	1

Number of subjects in period 2[1]	Sequence 4 (Placebo, Then VX-371 + placebo): VX-371 + placebo
Started	24
Completed	24
Not completed	0

Other noncompliance	-
Requires prohibited medication	-
Adverse event	-
Unspecified	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Not all the subjects who completed treatment period 1 entered treatment period 2. That is why the number of subjects starting treatment period 2 is not consistent with the number of subjects completing the treatment period 1.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period 1

Reporting group description: -

Reporting group values	Treatment Period 1	Total	
Number of subjects	142	142	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	23.3		
standard deviation	± 9.08	-	
Gender categorical Units: Subjects			
Female	55	55	
Male	87	87	

End points

End points reporting groups

Reporting group title	Sequence 1 (VX-371 + HS, Then HS): VX-371 + HS
Reporting group description:	
Subjects received VX-371 in combination with 3 milliliter (mL) 4.2% hypertonic saline (HS) in treatment period 1 followed by HS alone in treatment period 2.	
Reporting group title	Sequence 2 (HS, Then VX-371 + HS): HS
Reporting group description:	
Subjects received 3 mL 4.2% HS in treatment period 1 followed by VX-371 in combination with 3 mL 4.2% HS in treatment period 2.	
Reporting group title	Sequence 3 (VX-371 + placebo, then placebo): VX-371 + placebo
Reporting group description:	
Subjects received VX-371 in combination with placebo (0.17% saline) in treatment period 1 followed by placebo (0.17% saline) alone in treatment period 2.	
Reporting group title	Sequence 4 (Placebo, Then VX-371 + placebo): Placebo
Reporting group description:	
Subjects received placebo (0.17% saline) in treatment period 1 followed by VX-371 in combination with placebo (0.17% saline) in treatment period 2.	
Reporting group title	Sequence 1 (VX-371 + HS, Then HS): HS
Reporting group description:	
Subjects received VX-371 in combination with 3 mL 4.2% HS in treatment period 1 followed by HS alone in treatment period 2.	
Reporting group title	Sequence 2 (HS, Then VX-371 + HS): VX-371 + HS
Reporting group description:	
Subjects received 3 mL 4.2% HS in treatment period 1 followed by VX-371 in combination with 3 mL 4.2% HS in treatment period 2.	
Reporting group title	Sequence 3 (VX-371 + placebo, then placebo): Placebo
Reporting group description:	
Subjects received VX-371 in combination with placebo (0.17% saline) in treatment period 1 followed by placebo (0.17% saline) alone in treatment period 2.	
Reporting group title	Sequence 4 (Placebo, Then VX-371 + placebo): VX-371 + placebo
Reporting group description:	
Subjects received placebo (0.17% saline) in treatment period 1 followed by VX-371 in combination with placebo (0.17% saline) in treatment period 2.	
Subject analysis set title	VX-371 + HS
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received VX-371 in combination with 3 mL 4.2% hypertonic saline (HS) in treatment period 1 or 2.	
Subject analysis set title	Hypertonic Solution (HS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received 3 mL 4.2% HS in treatment period 1 or 2.	
Subject analysis set title	VX-371 + placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received VX-371 in combination with placebo (0.17% saline) in treatment period 1 or 2.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received placebo (0.17% saline) in treatment period 1 or 2	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

End point type	Primary

End point timeframe:

Baseline up to Day 143

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	VX-371 + HS	Hypertonic Solution (HS)	VX-371 + placebo	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	89	90	46	42
Units: Subjects				
Subjects with AEs	65	66	32	28
Subjects with SAEs	8	4	6	3

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 second (ppFEV1) at Day 28 of Each Treatment Period

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 second (ppFEV1) at Day 28 of Each Treatment Period

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.

End point type	Primary

End point timeframe:

Baseline, Day 28

End point values	VX-371 + HS	Hypertonic Solution (HS)	VX-371 + placebo	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	79	77	43	38
Units: percentage points				
least squares mean (confidence interval 95%)	0.1 (-1.5 to 1.6)	-0.1 (-1.7 to 1.4)	-0.8 (-2.9 to 1.2)	0.8 (-1.4 to 3.0)

Statistical analyses

Statistical analysis title	VX-371 + Hypertonic saline (HS) vs HS

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 79 for " VX-371 + Hypertonic saline (HS)" arm and 77 for "HS" arm . "Number of subjects included in analysis = 156" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	VX-371 + HS v Hypertonic Solution (HS)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8173
Method	Mixed Model Repeated Measure (MMRM)
Parameter estimate	Least Square (LS) mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.8

Statistical analysis title	VX-371+HS vs VX-371+Placebo

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 79 for "VX-371 + HS" arm and 43 for "VX-371 + Placebo" arm. "Number of subjects included in analysis = 122" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	VX-371 + HS v VX-371 + placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4962
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	3.5

Statistical analysis title	VX-371+HS vs Placebo

Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 79 for " VX-371 + Hypertonic saline (HS)" arm and 38 for "Placebo" arm. "Number of subjects included in analysis = 117" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	Placebo v VX-371 + HS

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5917
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	1.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Day 143	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	VX-371 + Hypertonic saline (HS)
Reporting group description: -	
Reporting group title	Hypertonic saline (HS)
Reporting group description: -	
Reporting group title	VX-371 + Placebo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	VX-371 + Hypertonic saline (HS)	Hypertonic saline (HS)	VX-371 + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 89 (8.99%)	4 / 90 (4.44%)	6 / 46 (13.04%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (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
Surgical and medical procedures			
Cystic fibrosis respiratory infection suppression			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (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
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (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
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	0 / 46 (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
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 89 (0.00%)	2 / 90 (2.22%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	3 / 89 (3.37%)	3 / 90 (3.33%)	5 / 46 (10.87%)
occurrences causally related to treatment / all	0 / 3	1 / 3	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 42 (7.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cystic fibrosis respiratory infection suppression			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Testicular torsion			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	VX-371 + Hypertonic saline (HS)	Hypertonic saline (HS)	VX-371 + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 89 (55.06%)	55 / 90 (61.11%)	26 / 46 (56.52%)
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Alanine aminotransferase increased			

subjects affected / exposed	3 / 89 (3.37%)	5 / 90 (5.56%)	0 / 46 (0.00%)
occurrences (all)	3	5	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 89 (6.74%)	8 / 90 (8.89%)	2 / 46 (4.35%)
occurrences (all)	6	8	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 89 (1.12%)	5 / 90 (5.56%)	5 / 46 (10.87%)
occurrences (all)	1	5	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 89 (5.62%)	4 / 90 (4.44%)	2 / 46 (4.35%)
occurrences (all)	5	4	2
Nausea			
subjects affected / exposed	2 / 89 (2.25%)	3 / 90 (3.33%)	3 / 46 (6.52%)
occurrences (all)	2	3	3
Vomiting			
subjects affected / exposed	1 / 89 (1.12%)	6 / 90 (6.67%)	1 / 46 (2.17%)
occurrences (all)	1	6	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 89 (22.47%)	13 / 90 (14.44%)	13 / 46 (28.26%)
occurrences (all)	29	13	15
Oropharyngeal pain			
subjects affected / exposed	8 / 89 (8.99%)	6 / 90 (6.67%)	4 / 46 (8.70%)
occurrences (all)	9	6	4
Nasal congestion			
subjects affected / exposed	7 / 89 (7.87%)	5 / 90 (5.56%)	2 / 46 (4.35%)
occurrences (all)	8	5	3
Respiration abnormal			
subjects affected / exposed	7 / 89 (7.87%)	6 / 90 (6.67%)	3 / 46 (6.52%)
occurrences (all)	7	8	3
Wheezing			
subjects affected / exposed	6 / 89 (6.74%)	2 / 90 (2.22%)	0 / 46 (0.00%)
occurrences (all)	6	2	0

Haemoptysis			
subjects affected / exposed	5 / 89 (5.62%)	6 / 90 (6.67%)	5 / 46 (10.87%)
occurrences (all)	5	10	5
Sputum increased			
subjects affected / exposed	5 / 89 (5.62%)	2 / 90 (2.22%)	5 / 46 (10.87%)
occurrences (all)	5	2	5
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	8 / 89 (8.99%)	12 / 90 (13.33%)	6 / 46 (13.04%)
occurrences (all)	9	13	6
Nasopharyngitis			
subjects affected / exposed	0 / 89 (0.00%)	5 / 90 (5.56%)	2 / 46 (4.35%)
occurrences (all)	0	5	2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 42 (47.62%)		
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	7		
Oropharyngeal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Respiration abnormal			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Sputum increased			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2016	- Corrected the study restrictions for diuretics and renin-angiotensive drugs - Contraception language changed to align with regulatory requirements

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported