



## 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	01 September 2017

#### Results information

Result version number	v2 (current)
This version publication date	04 December 2021
First version publication date	29 April 2018
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> To maintain the consistency with CT.gov results, EU results will be updated.

#### Trial information

##### Trial identification

Sponsor protocol code	VX15-371-101
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Parion Sciences
Sponsor organisation address	2800 Meridian Parkway, Durham NC, United States, 27713
Public contact	Anita Woodring, Parion Sciences, +1 919-313-1187, awoodring@parion.com
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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	12 October 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 September 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 ( $\geq$ ) 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	United States: 92
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Ireland: 12
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
<b>Arm title</b>	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.

<b>Arm title</b>	Sequence 2 (HS, Then VX-371 + HS): HS
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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.

<b>Arm title</b>	Sequence 3 (VX-371 + placebo, then placebo): VX-371 + placebo
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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.

<b>Arm title</b>	Sequence 4 (Placebo, Then VX-371 + placebo): Placebo
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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
<b>Arm title</b>	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.

<b>Arm title</b>	Sequence 2 (HS, Then VX-371 + HS): VX-371 + HS
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### 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.

<b>Arm title</b>	Sequence 3 (VX-371 + placebo, then placebo): Placebo
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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.

<b>Arm title</b>	Sequence 4 (Placebo, Then VX-371 + placebo): VX-371 + placebo
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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 <sup>[1]</sup>	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 <sup>[1]</sup>	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	-

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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
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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	
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	139	139	
More than one race	0	0	
Unknown or Not Reported	2	2	
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	139	139	
Unknown or Not Reported	3	3	

## 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 + Hypertonic Saline
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects received 85 mcg VX-371 diluted in 3 mL 4.2% HS through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.	
Subject analysis set title	Hypertonic Saline
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects received 3 mL 4.2% HS through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.	
Subject analysis set title	VX-371 + Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects received 85 mcg VX-371 diluted in 3 mL 0.17% saline (placebo) through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received 3 mL 0.17% saline (placebo) through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.

### **Primary: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs**

End point title	Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs <sup>[1]</sup>
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. AEs included abnormal clinically significant findings for spirometry, clinical laboratory parameters, standard 12-lead electrocardiograms (ECGs), vital signs and ophthalmologic examinations. Serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 112 days (up to 28 days after last dose) that were absent before treatment or that worsened relative to pretreatment state. TEAEs included both serious and non-serious TEAEs. Safety set included all subjects who received at least 1 dose of inhaled study drug.

End point type	Primary
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End point timeframe:

Baseline (Day 1) up to 28 days post last administration of study drug (up to 112 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	VX-371 + Hypertonic Saline	Hypertonic Saline	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 TEAEs	65	66	32	28
Subjects With Serious TEAEs	8	4	6	3

### **Statistical analyses**

No statistical analyses for this end point

### **Primary: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 28**

End point title	Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 28
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Study Baseline was defined as the most recent non-missing measurement before the first dose of inhaled study drug in the study. Day 28 measurements after treatment discontinuation from the treatment period in which discontinuation occurred were included in the analysis. The full analysis set (FAS) included all randomised subjects who carried the intended homozygous F508del-cystic fibrosis transmembrane conductance regulator (CFTR) mutation and received at least 1 dose of inhaled study drug. Here, "Number of subjects analysed" signifies subjects evaluable for this endpoint.

End point type	Primary
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End point timeframe:

Study baseline, Day 28

End point values	VX-371 + Hypertonic Saline	Hypertonic Saline	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 (standard error)	0.1 (± 0.8)	-0.1 (± 0.8)	-0.8 (± 1.1)	0.8 (± 1.1)

## Statistical analyses

Statistical analysis title	VX-371 + Hypertonic Saline Vs Hypertonic Saline
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" arm and 77 for "Hypertonic saline" 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 + Hypertonic Saline v Hypertonic Saline
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8173
Method	Mixed-effects Model for Repeated Measure
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 + Placebo Vs Hypertonic Saline
Statistical analysis description:	
As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 43 for "VX-371 + Placebo" arm and 77 for "Hypertonic Saline" arm . "Number of subjects included in analysis = 120" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.	
Comparison groups	VX-371 + Placebo v Hypertonic Saline
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5903
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	LS mean difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	1.9

<b>Statistical analysis title</b>	VX-371 + Hypertonic Saline Vs Placebo
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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" 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	VX-371 + Hypertonic Saline v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5917
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	1.9

<b>Statistical analysis title</b>	Hypertonic Saline Vs Placebo
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Statistical analysis description:

As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 77 for "Hypertonic saline (HS)" arm and 38 for "Placebo" arm. "Number of subjects included in analysis = 115" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.

Comparison groups	Hypertonic Saline v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5021
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	LS mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	1.8

<b>Statistical analysis title</b>	VX-371 + Placebo Vs Placebo
Statistical analysis description:	
As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 43 for " VX-371 + Placebo" arm and 38 for "Placebo" arm . "Number of subjects included in analysis =81" is reflected due to EudraCT database limitation of summing up the comparison arm numbers.	
Comparison groups	VX-371 + Placebo v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1382
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	LS mean difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	0.5

<b>Statistical analysis title</b>	VX-371 + Hypertonic Saline, VX-371 + Placebo
Comparison groups	VX-371 + Hypertonic Saline v VX-371 + Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.4962
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	LS mean difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	3.5

Notes:

[2] - As this is a cross-over study, actual number of subjects analysed for the statistical comparison was 79 for "VX-371 + Hypertonic Saline" 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.

## Secondary: Plasma Concentrations of VX-371

End point title	Plasma Concentrations of VX-371
End point description:	
The Pharmacokinetic (PK) analysis set included all subjects who received at least 1 dose of VX-371. Here, "Number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies those subjects who were evaluable at specified time points.	
End point type	Secondary
End point timeframe:	
Pre-dose (90 minutes prior inhaled study drug administration) and 60 minutes post-dose on Days 1, 14 and 28 within treatment period 1 and 2	

End point values	VX-371 + Hypertonic Saline	VX-371 + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	45		
Units: picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Day 1: Pre-dose (n =89, 44)	0.00 (± 0.00)	0.18 (± 1.17)		
Day 1: Post-dose (n =87, 44)	2.57 (± 2.35)	5.64 (± 4.27)		
Day 14: Pre-dose (n =86, 43)	1.63 (± 3.06)	2.77 (± 4.77)		
Day 14: Post-dose (n =81, 42)	5.81 (± 5.44)	11.0 (± 9.74)		
Day 28: Pre-dose (n =86, 45)	2.68 (± 4.75)	3.67 (± 5.59)		
Day 28: Post-dose (n =82, 43)	6.41 (± 6.92)	10.9 (± 9.48)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Urine Concentrations of VX-371

End point title	Urine Concentrations of VX-371
End point description:	
The PK analysis set included all subjects who received at least 1 dose of VX-371. Here, "Number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies those subjects who were evaluable at specified time points.	
End point type	Secondary
End point timeframe:	
Pre-dose (90 minutes prior inhaled study drug administration) and 60 minutes post-dose on Days 1, 14 and 28 within treatment period 1 and 2	

End point values	VX-371 + Hypertonic Saline	VX-371 + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	45		
Units: pg/mL				
arithmetic mean (standard deviation)				
Day 1: Pre-dose (n =88, 45)	0.0745 (± 0.699)	0.00 (± 0.00)		
Day 1: Post-dose (n =88, 45)	7.78 (± 11.8)	22.1 (± 38.4)		
Day 14: Pre-dose (n =85, 43)	41.0 (± 97.2)	69.6 (± 107)		
Day 14: Post-dose (n =83, 42)	38.9 (± 64.8)	75.0 (± 98.7)		
Day 28: Pre-dose (n =84, 45)	65.3 (± 155)	98.6 (± 175)		
Day 28: Post-dose (n =82, 43)	49.1 (± 120)	75.1 (± 108)		

## **Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days post last administration of study drug, up to 112 days

Adverse event reporting additional description:

Safety set included all subjects who received at least 1 dose of inhaled study drug.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	VX-371 + Hypertonic saline (HS)
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Reporting group description:

Subjects received 85 mcg VX-371 diluted in 3 mL 4.2% HS through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.

Reporting group title	Hypertonic saline (HS)
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Reporting group description:

Subjects received 3 mL 4.2% HS through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.

Reporting group title	VX-371 + Placebo
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Reporting group description:

Subjects received 85 mcg VX-371 diluted in 3 mL 0.17% saline (placebo) through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.

Reporting group title	Placebo
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Reporting group description:

Subjects received 3 mL 0.17% saline (placebo) through oral nebulized inhalation twice daily for 28 days in either treatment period 1 or 2.

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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			

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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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

<b>Serious adverse events</b>	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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
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 %

<b>Non-serious adverse events</b>	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			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 89 (3.37%)	5 / 90 (5.56%)	0 / 46 (0.00%)
occurrences (all)	3	5	0
Nervous system disorders			
Headache			
alternative assessment type: Systematic			

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

Systematic			
subjects affected / exposed	7 / 89 (7.87%)	6 / 90 (6.67%)	3 / 46 (6.52%)
occurrences (all)	7	8	3
Wheezing			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 89 (6.74%)	2 / 90 (2.22%)	0 / 46 (0.00%)
occurrences (all)	6	2	0
Haemoptysis			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 89 (5.62%)	6 / 90 (6.67%)	5 / 46 (10.87%)
occurrences (all)	5	10	5
Sputum increased			
alternative assessment type: Systematic			
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			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 89 (8.99%)	12 / 90 (13.33%)	6 / 46 (13.04%)
occurrences (all)	9	13	6
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 89 (0.00%)	5 / 90 (5.56%)	2 / 46 (4.35%)
occurrences (all)	0	5	2

<b>Non-serious adverse events</b>	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 42 (47.62%)		
Investigations			
Pulmonary function test decreased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4		
Nervous system disorders Headache alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
General disorders and administration site conditions Pyrexia alternative assessment type: Systematic subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5		
Gastrointestinal disorders Diarrhoea alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Nausea alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Vomiting alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1  0 / 42 (0.00%) 0  0 / 42 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Oropharyngeal pain alternative assessment type: Systematic subjects affected / exposed occurrences (all)  Nasal congestion	5 / 42 (11.90%) 7  1 / 42 (2.38%) 1		



alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Respiration abnormal alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Wheezing alternative assessment type: Systematic subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Haemoptysis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5		
Sputum increased alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Nasopharyngitis alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2016	<ul style="list-style-type: none"><li>- Corrected the study restrictions for diuretics and renin-angiotensive drugs</li><li>- Contraception language changed to align with regulatory requirements</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported