



Clinical trial results:

A Phase 2a, Two-part, Randomized, Double-blind, Placebo-controlled, Incomplete Block Crossover Study to Evaluate the Safety and Efficacy of VX-371 Solution for Inhalation With and Without Oral Ivacaftor in Subjects With Primary Ciliary Dyskinesia

Summary

EudraCT number	2015-004917-26
Trial protocol	DE DK NL PL GB IT
Global end of trial date	20 November 2018

Results information

Result version number	v2 (current)
This version publication date	27 January 2022
First version publication date	02 June 2019
Version creation reason	<ul style="list-style-type: none">• New data added to full data set• Correction of full data set New Primary and secondary endpoints added.

Trial information

Trial identification

Sponsor protocol code	PS-G202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02871778
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Parion Sciences
Sponsor organisation address	2800 Meridian Parkway, Durham, NC, United States, 27713
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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	06 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2018
Global end of trial reached?	Yes
Global end of trial date	20 November 2018
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 Part A and ivacaftor (IVA) with VX-371 in Part B, administered with and without 4.2% hypertonic saline (HS) in subjects with primary ciliary dyskinesia (PCD) who are ≥ 12 years of age.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 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	Netherlands: 7
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	123
EEA total number of subjects	71

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)	36
Adults (18-64 years)	87
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with PCD greater than 12 years of age were enrolled in the study. Subjects with cystic fibrosis (CF) or only 1 mutation in the CF transmembrane regulator (CFTR) gene and a sweat chloride test ≥ 60 millimoles by quantitative pilocarpine iontophoresis were excluded.

Pre-assignment

Screening details:

This study included 2 parts (Part A and B). Part A consisted of 2 treatment periods (Treatment Period 1 and 2) separated by a 28-day Washout Period. Part B (optional) consisted of one treatment period (Treatment Period 3). Subjects who enrolled in Part B received IVA in addition to the treatment they were receiving in Treatment Period 2 of Part A.

Period 1

Period 1 title	Part A (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
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Arm title	Part A: VX-371 in hypertonic saline (HS)
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Arm description:

Subjects received VX-371 in 4.2% HS in treatment period 1.

Arm type	Experimental
Investigational medicinal product name	VX-371
Investigational medicinal product code	P-1037
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received VX-371 in 4.2% HS twice daily from Day 1 through Day 29 in treatment period 1.

Arm title	Part A: Hypertonic saline (HS)
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Arm description:

Subjects received 4.2% HS in treatment period 1.

Arm type	Experimental
Investigational medicinal product name	hypertonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received 4.2% HS twice daily from Day 1 through Day 29 in treatment period 1.

Arm title	Part A: VX-371
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Arm description:

Subjects received VX-371 in 0.17% saline in treatment period 1.

Arm type	Experimental
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Investigational medicinal product name	VX-371
Investigational medicinal product code	P-1037
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received VX-371 in 0.17% saline twice daily from Day 1 through Day 29 in treatment period 1.

Arm title	Part A: Placebo
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Arm description:

Subjects received Placebo (0.17% saline) in treatment period 1.

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:

Subjects received Placebo (0.17% saline) twice daily from Day 1 through Day 29 in treatment period 1.

Number of subjects in period 1	Part A: VX-371 in hypertonic saline (HS)	Part A: Hypertonic saline (HS)	Part A: VX-371
Started	43	41	21
Completed	40	37	18
Not completed	3	4	3
Non-Compliance with Study Drug	-	-	1
Other	-	1	1
Adverse event	1	1	1
Withdrawal of Consent (not due to AE)	2	2	-

Number of subjects in period 1	Part A: Placebo
Started	18
Completed	16
Not completed	2
Non-Compliance with Study Drug	-
Other	-
Adverse event	-
Withdrawal of Consent (not due to AE)	2

Period 2

Period 2 title	Part A (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
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Arm title	Part A: Hypertonic Saline (HS)
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Arm description:

Subjects who received VX-371 in 4.2% HS in treatment period 1, followed by a washout period, received 4.2% HS in treatment period 2.

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

Dosage and administration details:

Subjects received 4.2% HS twice daily from Day 57 through Day 85 in treatment period 2.

Arm title	Part A: VX-371 in HS
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Arm description:

Subjects who received 4.2% HS in treatment period 1, followed by a washout period, received VX-371 in 4.2% HS in treatment period 2.

Arm type	Experimental
Investigational medicinal product name	VX-371
Investigational medicinal product code	P-1037
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received VX-371 in 4.2% HS twice daily from Day 57 through Day 85 in treatment period 2.

Arm title	Part A: Placebo
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Arm description:

Subjects who received VX-371 in 0.17% saline in treatment period 1, followed by a washout period, received 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:

Subjects received Placebo (0.17% saline) twice daily from Day 57 through Day 85 in treatment period 2.

Arm title	Part A: VX-371
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Arm description:

Subjects who received Placebo (0.17% saline) in treatment period 1, followed by a washout period, received VX-371 in 0.17% saline in treatment period 2..

Arm type	Experimental
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Investigational medicinal product name	VX-371
Investigational medicinal product code	P-1037
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received VX-371 in 0.17% saline twice daily from Day 57 through Day 85 in treatment period 2.

Number of subjects in period 2	Part A: Hypertonic Saline (HS)	Part A: VX-371 in HS	Part A: Placebo
Started	40	37	18
Completed	37	35	17
Not completed	3	2	1
Non-Compliance with Study Drug	1	-	1
Adverse event	2	2	-
Lost to follow-up	-	-	-

Number of subjects in period 2	Part A: VX-371
Started	16
Completed	15
Not completed	1
Non-Compliance with Study Drug	-
Adverse event	-
Lost to follow-up	1

Period 3

Period 3 title	Part B (Treatment period 3)
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	Part B: VX-371 in HS + Ivacaftor

Arm description:

Subjects who received VX-371 in 4.2% HS in treatment period 2, received VX-371 in 4.2% HS and IVA in optional treatment period 3.

Arm type	Experimental
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Investigational medicinal product name	VX-371
Investigational medicinal product code	P-1037
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Subjects received VX-371 in 4.2% HS twice daily from Day 85 through Day 113 in treatment period 3.	
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA tablet orally twice daily from Day 85 through Day 113 in treatment period 3.	
Arm title	Part B: HS + Ivacaftor
Arm description:	
Subjects who received 4.2% HS in treatment period 2, received 4.2% HS and IVA in optional treatment period 3.	
Arm type	Experimental
Investigational medicinal product name	hypertonic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Subjects received 4.2% HS twice daily from Day 85 through Day 113 in treatment period 3.	
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA twice daily from Day 85 through Day 113 in treatment period 3.	
Arm title	Part B: VX-371 + Ivacaftor
Arm description:	
Subjects who received VX-371 in 0.17% saline in treatment period 2, received VX-371 in 0.17% saline and IVA in optional treatment period 3.	
Arm type	Experimental
Investigational medicinal product name	VX-371
Investigational medicinal product code	P-1037
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Subjects received VX-371 in 0.17% saline twice daily from Day 85 through Day 113 in treatment period 3.	
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA twice daily from Day 85 through Day 113 in treatment period 3.

Arm title	Part B: Placebo + Ivacaftor
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Arm description:

Subjects who received Placebo (0.17% saline) in treatment period 2, received Placebo (0.17% saline) and IVA in optional treatment period 3.

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:

Subjects received Placebo (0.17% saline) twice daily from Day 85 through Day 113 in treatment period 3.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA twice daily from Day 85 through Day 113 in treatment period 3.

Number of subjects in period 3^[1]	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor
Started	11	27	7
Completed	10	26	6
Not completed	1	1	1
Adverse event	1	1	1

Number of subjects in period 3^[1]	Part B: Placebo + Ivacaftor
Started	12
Completed	12
Not completed	0
Adverse event	-

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: Out of 104 subjects who completed Part A, 57 subjects rolled-over to optional Part B.

Baseline characteristics

Reporting groups

Reporting group title	Part A (Treatment period 1)
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Reporting group description:

All subjects who received at least 1 dose of study drug during Part A were included for presenting Baseline Characteristics.

Reporting group values	Part A (Treatment period 1)	Total	
Number of subjects	123	123	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	27.80 ± 12.954	-	
Gender categorical Units: Subjects			
Female	78	78	
Male	45	45	

End points

End points reporting groups

Reporting group title	Part A: VX-371 in hypertonic saline (HS)
Reporting group description: Subjects received VX-371 in 4.2% HS in treatment period 1.	
Reporting group title	Part A: Hypertonic saline (HS)
Reporting group description: Subjects received 4.2% HS in treatment period 1.	
Reporting group title	Part A: VX-371
Reporting group description: Subjects received VX-371 in 0.17% saline in treatment period 1.	
Reporting group title	Part A: Placebo
Reporting group description: Subjects received Placebo (0.17% saline) in treatment period 1.	
Reporting group title	Part A: Hypertonic Saline (HS)
Reporting group description: Subjects who received VX-371 in 4.2% HS in treatment period 1, followed by a washout period, received 4.2% HS in treatment period 2.	
Reporting group title	Part A: VX-371 in HS
Reporting group description: Subjects who received 4.2% HS in treatment period 1, followed by a washout period, received VX-371 in 4.2% HS in treatment period 2.	
Reporting group title	Part A: Placebo
Reporting group description: Subjects who received VX-371 in 0.17% saline in treatment period 1, followed by a washout period, received Placebo (0.17% saline) in treatment period 2.	
Reporting group title	Part A: VX-371
Reporting group description: Subjects who received Placebo (0.17% saline) in treatment period 1, followed by a washout period, received VX-371 in 0.17% saline in treatment period 2..	
Reporting group title	Part B: VX-371 in HS + Ivacaftor
Reporting group description: Subjects who received VX-371 in 4.2% HS in treatment period 2, received VX-371 in 4.2% HS and IVA in optional treatment period 3.	
Reporting group title	Part B: HS + Ivacaftor
Reporting group description: Subjects who received 4.2% HS in treatment period 2, received 4.2% HS and IVA in optional treatment period 3.	
Reporting group title	Part B: VX-371 + Ivacaftor
Reporting group description: Subjects who received VX-371 in 0.17% saline in treatment period 2, received VX-371 in 0.17% saline and IVA in optional treatment period 3.	
Reporting group title	Part B: Placebo + Ivacaftor
Reporting group description: Subjects who received Placebo (0.17% saline) in treatment period 2, received Placebo (0.17% saline) and IVA in optional treatment period 3.	
Subject analysis set title	Part A: VX-371 in HS
Subject analysis set type	Full 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	Part A: HS

Subject analysis set type	Full 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	Part A: VX-371
Subject analysis set type	Full 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	Part A: Placebo
Subject analysis set type	Full 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: Part A: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Part A: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs ^[1]
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End point description:

An 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 pulse oximetry 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 84 days that were absent before treatment or that worsened relative to pretreatment state. TEAEs included both serious and non-serious TEAEs. Part A safety set included all subjects who received at least 1 dose of study drug in Part A.

End point type	Primary
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End point timeframe:

Part A: From first dose of study drug up 84 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: Only descriptive statistics were planned. No statistical comparisons were planned for primary safety end point.

End point values	Part A: VX-371 in HS	Part A: HS	Part A: VX-371	Part A: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	80	37	36
Units: Subjects				
Subjects with TEAEs	52	46	22	23
Subjects with Serious TEAEs	1	1	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Number of Subjects With TEAEs and Serious TEAEs

End point title	Part B: Number of Subjects With TEAEs and Serious TEAEs ^[2]
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End point description:

An 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 ECGs, vital signs and pulse oximetry examinations. 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 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. Part B safety set included all subjects who received at least 1 dose of ivacaftor in Part B.

End point type	Primary
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End point timeframe:

Part B: Day 85 up to 28 days after last dose of study drug (56 days)

Notes:

[2] - 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: Only descriptive statistics were planned. No statistical comparisons were planned for primary safety endpoint.

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	27	7	12
Units: Subjects				
Subjects with TEAEs	5	17	5	9
Subjects with Serious TEAEs	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 29

End point title	Part A: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 29
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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. The study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the study. Part A full analysis set (FAS) included all randomized subjects who received at least 1 dose of study drug in Part A and had a confirmed diagnosis of primary ciliary dyskinesia (PCD). Here, "number of subjects analysed" signifies subjects evaluable for this endpoint.

End point type	Primary
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End point timeframe:

Part A: Study Baseline, Day 29 of each treatment period

End point values	Part A: VX-371 in HS	Part A: HS	Part A: VX-371	Part A: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	75	34	34
Units: Percentage of predicted FEV1				
least squares mean (standard error)	0.989 (\pm 0.7097)	-0.531 (\pm 0.7202)	-0.491 (\pm 1.0736)	-1.329 (\pm 1.0730)

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
For 'number of subjects included in the analysis' field: total number of subjects analysed were 78 for VX-371 in HS arm and 75 for HS arm instead of 153 subjects because this study is a cross-over design and same subjects may have received both the interventions.	
Comparison groups	Part A: VX-371 in HS v Part A: HS
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0437
Method	Mixed-effects Model
Parameter estimate	Least Square (LS) Mean difference
Point estimate	1.519
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	2.995

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
For 'number of subjects included in the analysis' field: total number of subjects analysed were 75 for Part A: HS arm and 34 for Part A: VX-371 arm instead of 109 subjects because this study is a cross-over design and same subjects may have received both the interventions.	
Comparison groups	Part A: HS v Part A: VX-371
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9755
Method	Mixed-effects Model
Parameter estimate	LS Mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.509
upper limit	2.589

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
For 'number of subjects included in the analysis' field: total number of subjects analysed were 78 for Part A: VX-371 in HS arm and 34 for Part A: Placebo arm instead of 112 subjects because this study is a cross-over design and same subjects may have received both the interventions.	
Comparison groups	Part A: VX-371 in HS v Part A: Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0731
Method	Mixed-effects Model
Parameter estimate	LS Mean difference
Point estimate	2.318
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	4.856

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
For 'number of subjects included in the analysis' field: total number of subjects analysed were 75 for Part A: HS arm and 34 for Part A: Placebo arm instead of 109 subjects because this study is a cross-over design and same subjects may have received both the interventions.	
Comparison groups	Part A: HS v Part A: Placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5373
Method	Mixed-effects Model
Parameter estimate	LS Mean Difference
Point estimate	0.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.751
upper limit	3.348

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
For 'number of subjects included in the analysis' field: total number of subjects analysed were 34 for VX-371 arm and Placebo arm instead of 68 subjects because this study is a cross-over design and same subjects may have received both the interventions.	

Comparison groups	Part A: VX-371 v Part A: Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.453
Method	Mixed-effects Model
Parameter estimate	LS Mean difference
Point estimate	0.838
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.368
upper limit	3.045

Notes:

[3] - For 'number of subjects included in the analysis' field: total number of subjects analysed were 34 for Part A: VX-371 arm and 34 for Part A: Placebo arm instead of 68 subjects because this study is a cross-over design and same subjects may have received both the interventions.

Primary: Part B: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 29

End point title	Part B: Absolute Change From Study Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 29 ^[4]
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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. The study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the study. Part B FAS included all subjects who had a confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. 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 29 of Part B

Notes:

[4] - 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: The endpoint for Part B was designed to perform within group statistical comparison. Because only between treatment statistical comparisons can be reported in the EudraCT database, no statistical analyses are reported for Part B endpoint.

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	26	6	12
Units: Percentage of predicted FEV1				
least squares mean (standard error)				
Change from study baseline	4.721 (± 1.9314)	1.722 (± 1.1976)	-0.592 (± 2.5011)	-0.965 (± 1.8388)

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Absolute Change From Part B Baseline in Percent Predicted Forced

Expiratory Volume in 1 Second (ppFEV1) at Day 29

End point title	Part B: Absolute Change From Part B Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Day 29 ^[5]
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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. Part B baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ivacaftor in Part B and after the last dose in Period 2. Part B FAS included all subjects who had a confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Primary
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End point timeframe:

Part B Baseline, Day 29 of Part B

Notes:

[5] - 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: The endpoint for Part B was designed to perform within group statistical comparison. Because only between treatment statistical comparisons can be reported in the EudraCT database, no statistical analyses are reported for Part B endpoint.

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	26	6	12
Units: Percentage of predicted FEV1				
least squares mean (standard error)	2.528 (± 1.8633)	1.678 (± 1.1414)	-1.018 (± 2.3797)	-2.040 (± 1.7427)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Study Baseline in Quality of Life-Primary Ciliary Dyskinesia (QOL-PCD) (Adult Version) Lower Respiratory Symptoms Domain Score at Day 29

End point title	Part A: Change From Study Baseline in Quality of Life-Primary Ciliary Dyskinesia (QOL-PCD) (Adult Version) Lower Respiratory Symptoms Domain Score at Day 29
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End point description:

QOL- PCD adult version has following 10 domains: lower respiratory symptoms, emotional functioning, treatment burden, role, social functioning, vitality, health perception, upper respiratory symptoms, physical functioning and hearing symptoms. Total numbers of items in lower respiratory symptoms domain are 6 in questionnaire for adults. All items are scored using a 4-point Likert scale. Scaled score calculated as: $[\text{Sum of scores} - (n \times 1)] / [(n \times 4) - (n \times 1)] \times 100$. Where 'n' is number of questions in domain. Total score range is from 0-100, where higher score indicates greater improvement. Change from study baseline >0 indicated improvement. Study baseline is defined as most recent non-missing measurement (scheduled or unscheduled) collected before first dose of study drug in study. Part B FAS included all subjects who had a confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. "Number of subjects analysed" signifies adult subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Study Baseline, Day 29 of Part A

End point values	Part A: VX-371 in HS	Part A: HS	Part A: VX-371	Part A: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	45	17	15
Units: score on a scale				
arithmetic mean (standard deviation)	4.23 (± 18.076)	3.58 (± 16.715)	0.98 (± 12.915)	7.04 (± 16.728)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Study Baseline in Quality of Life-Primary Ciliary Dyskinesia (QOL-PCD) (Adult Version) Lower Respiratory Symptoms Domain Score at Day 29

End point title	Part B: Change From Study Baseline in Quality of Life-Primary Ciliary Dyskinesia (QOL-PCD) (Adult Version) Lower Respiratory Symptoms Domain Score at Day 29
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End point description:

QOL- PCD adult version has following 10 domains: lower respiratory symptoms, emotional functioning, treatment burden, role, social functioning, vitality, health perception, upper respiratory symptoms, physical functioning and hearing symptoms. Total numbers of items in lower respiratory symptoms domain are 6 in questionnaire for adults. All items are scored using a 4-point Likert scale. Scaled score calculated as: $[\text{Sum of scores} - (n \times 1)] / [(n \times 4) - (n \times 1)] \times 100$. Where 'n' is number of questions in domain. The total score range is from 0-100, where higher score indicates greater improvement. Change from study baseline >0 indicated improvement. Study baseline is defined as most recent non-missing measurement (scheduled or unscheduled) collected before first dose of study drug in study. Part B FAS included all subjects who had confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. "Number of subjects analysed" signifies adult subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Study Baseline, Day 29 of Part B

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	16	3	6
Units: score on a scale				
arithmetic mean (standard deviation)	16.67 (± 14.487)	1.39 (± 17.153)	7.41 (± 3.208)	-5.56 (± 23.307)

Statistical analyses

Secondary: Part B: Change From Part B Baseline in Quality of Life-Primary Ciliary Dyskinesia (QOL-PCD) (Adult Version) Lower Respiratory Symptoms Domain Score at Day 29

End point title	Part B: Change From Part B Baseline in Quality of Life-Primary Ciliary Dyskinesia (QOL-PCD) (Adult Version) Lower Respiratory Symptoms Domain Score at Day 29
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End point description:

QOL- PCD adult version has following 10 domains: lower respiratory symptoms, emotional functioning, treatment burden, role, social functioning, vitality, health perception, upper respiratory symptoms, physical functioning and hearing symptoms. Total numbers of items in lower respiratory symptoms domain are 6 in questionnaire for adults. All items are scored using a 4-point Likert scale. Scaled score calculated as: $[\text{Sum of scores} - (n*1)] / [(n*4) - (n*1)]*100$. Where 'n' is number of questions in domain. Total score range is from 0-100, where higher score indicates greater improvement. Change from Part B baseline >0 indicated improvement. Part B baseline was defined as most recent non-missing measurement (scheduled or unscheduled) collected before first dose of ivacaftor in Part B and after last dose in Period 2. Part B FAS was analysed. "Number of subjects analysed" =adult subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Part B Baseline, Day 29 of Part B

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	16	3	6
Units: score on a scale				
arithmetic mean (standard deviation)	11.11 (± 15.713)	1.39 (± 19.928)	5.56 (± 16.667)	-7.41 (± 10.344)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Study Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score for Subjects Aged Greater Than or Equals to (>=) 16 Years at Day 29

End point title	Part A: Change From Study Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score for Subjects Aged Greater Than or Equals to (>=) 16 Years at Day 29
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End point description:

SGRQ measured health-related quality of life among subjects with respiratory diseases. It is a 40 items questionnaire grouped into three domains (Symptoms, Activity, and Impacts). Total scores range from 0 to 100. Higher score reflected worse quality of life. The study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the study. Part A FAS included all randomized subjects who received at least 1 dose of study drug in Part A and had a confirmed diagnosis of PCD. Here, "Number of subjects analysed" signifies subjects >=16 years of age who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Study Baseline, Day 29 of Part A

End point values	Part A: VX-371 in HS	Part A: HS	Part A: VX-371	Part A: Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	28	25
Units: score on a scale				
arithmetic mean (standard deviation)	-1.28 (\pm 8.452)	-2.17 (\pm 6.462)	1.54 (\pm 8.576)	-1.52 (\pm 9.082)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Study Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score for subjects Aged ≥ 16 Years at Day 29

End point title	Part B: Change From Study Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score for subjects Aged ≥ 16 Years at Day 29
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End point description:

SGRQ measured health-related quality of life among subjects with respiratory diseases. It is a 40 items questionnaire grouped into three domains (Symptoms, Activity, and Impacts). Total scores range from 0 to 100. Higher score reflected worse quality of life. The study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the study. Part B FAS included all subjects who had a confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. Here, "number of subjects analysed" signifies subjects ≥ 16 years of age who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	Study Baseline, Day 29 of Part B

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	25	5	8
Units: score on a scale				
arithmetic mean (standard deviation)	-1.69 (\pm 7.442)	-6.87 (\pm 6.571)	0.78 (\pm 5.879)	4.52 (\pm 16.995)

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Change From Part B Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score for Subjects Aged ≥ 16 Years at Day 29

End point title	Part B: Change From Part B Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score for Subjects Aged ≥ 16 Years at Day 29
End point description: SGRQ measured health-related quality of life among subjects with respiratory diseases. It is a 40 items questionnaire grouped into three domains (Symptoms, Activity, and Impacts). Total scores range from 0 to 100. Higher score reflected worse quality of life. Part B baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of ivacaftor in Part B and after the last dose in Period 2. Part B FAS included all subjects who had a confirmed diagnosis of PCD and received at least 1 dose of ivacaftor in Part B. Here, "number of subjects analysed" signifies subjects ≥ 16 years of age who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Part B Baseline, Day 29 of Part B	

End point values	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	25	5	8
Units: score on a scale				
arithmetic mean (standard deviation)	-3.90 (\pm 4.331)	-2.64 (\pm 6.575)	0.97 (\pm 7.561)	3.19 (\pm 11.649)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: From first dose of study drug up to 84 days; Part B: Day 85 up to 28 days after last dose of study drug (56 days)

Adverse event reporting additional description:

Part A safety set included all subjects who received at least 1 dose of study drug in Part A. Part B safety set included all subjects who received at least 1 dose of ivacaftor in Part B.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Part A: VX-371 in 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	Part A: 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	Part A: VX-371
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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	Part A: 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.

Reporting group title	Part B: VX-371 in HS + Ivacaftor
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Reporting group description:

Subjects who were on 85 mcg VX-371 diluted in 3 mL 4.2% HS through oral nebulized inhalation twice daily for 28 days (from Day 57 through Day 85) in treatment period 2 continued their inhaled study drug regimen from Treatment Period 2 and also received ivacaftor 150 mg tablet twice daily for 28 days (from Day 85 through Day 113) in treatment period 3.

Reporting group title	Part B: HS + Ivacaftor
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Reporting group description:

Subjects who were on 3 mL 4.2% HS through oral nebulized inhalation twice daily for 28 days (from Day 57 through Day 85) in treatment period 2 continued their inhaled study drug regimen from Treatment Period 2 and also received ivacaftor 150 mg tablet twice daily for 28 days (from Day 85 through Day 113) in treatment period 3.

Reporting group title	Part B: VX-371 + Ivacaftor
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Reporting group description:

Subjects who were on 85 mcg VX-371 diluted in 3 mL 0.17% saline (placebo) through oral nebulized inhalation twice daily for 28 days (from Day 57 through Day 85) in treatment period 2 continued their inhaled study drug regimen from Treatment Period 2 and also received ivacaftor 150 mg tablet twice daily for 28 days (from Day 85 through Day 113) in treatment period 3.

Reporting group title	Part B: Placebo + Ivacaftor
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Reporting group description:

Subjects who were on 3 mL 0.17% saline (placebo) through oral nebulized inhalation twice daily for 28 days (from Day 57 through Day 85) in treatment period 2 continued their inhaled study drug regimen from Treatment Period 2 and also received ivacaftor 150 mg tablet twice daily for 28 days (from Day 85 through Day 113) in treatment period 3.

Serious adverse events	Part A: VX-371 in HS	Part A: Hypertonic Saline (HS)	Part A: VX-371
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	1 / 37 (2.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	0 / 37 (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
Haemoptysis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A: Placebo	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)	0 / 11 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			

subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 11 (0.00%)	0 / 27 (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
Lung disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: VX-371 in HS	Part A: Hypertonic Saline (HS)	Part A: VX-371
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 81 (49.38%)	27 / 80 (33.75%)	12 / 37 (32.43%)
Investigations			
Haemophilus test positive			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	3 / 37 (8.11%)
occurrences (all)	1	1	3
Moraxella test positive			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Lipase increased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Streptococcus test positive			

subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 9	3 / 80 (3.75%) 3	3 / 37 (8.11%) 4
Headache subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 10	7 / 80 (8.75%) 8	2 / 37 (5.41%) 3
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	6 / 80 (7.50%) 6	0 / 37 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 5	1 / 80 (1.25%) 1	2 / 37 (5.41%) 2
Fatigue subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	4 / 80 (5.00%) 4	2 / 37 (5.41%) 3
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Eye disorders Eye pruritus subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Vision blurred			

subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	1 / 37 (2.70%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 12	8 / 80 (10.00%) 8	4 / 37 (10.81%) 5
Oropharyngeal pain subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 8	3 / 80 (3.75%) 3	3 / 37 (8.11%) 3
Nasal congestion subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	3 / 80 (3.75%) 3	1 / 37 (2.70%) 1
Sputum increased			

subjects affected / exposed	5 / 81 (6.17%)	1 / 80 (1.25%)	0 / 37 (0.00%)
occurrences (all)	5	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 81 (0.00%)	0 / 80 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 80 (1.25%) 1	0 / 37 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4	1 / 80 (1.25%) 1	0 / 37 (0.00%) 0
Pseudomonas infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	0 / 80 (0.00%) 0	0 / 37 (0.00%) 0

Non-serious adverse events	Part A: Placebo	Part B: VX-371 in HS + Ivacaftor	Part B: HS + Ivacaftor
Total subjects affected by non-serious adverse events subjects affected / exposed	16 / 36 (44.44%)	5 / 11 (45.45%)	15 / 27 (55.56%)
Investigations			
Haemophilus test positive subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Moraxella test positive subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Amylase increased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Forced expiratory volume decreased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Hepatic enzyme increased			

subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 11 (9.09%) 1	0 / 27 (0.00%) 0
Streptococcus test positive subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	2 / 27 (7.41%) 2
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 6	3 / 11 (27.27%) 5	4 / 27 (14.81%) 9
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 11 (0.00%) 0	3 / 27 (11.11%) 3
Pyrexia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 11 (0.00%) 0	3 / 27 (11.11%) 4
Fatigue subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	2 / 11 (18.18%) 2	1 / 27 (3.70%) 1
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Eye disorders Eye pruritus			

subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 11 (0.00%) 0	5 / 27 (18.52%) 6
Abdominal pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	2 / 27 (7.41%) 3
Constipation subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	2 / 27 (7.41%) 2
Abdominal distension subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 11 (9.09%) 1	0 / 27 (0.00%) 0
Reproductive system and breast disorders			
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	0 / 27 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4	3 / 11 (27.27%) 3	2 / 27 (7.41%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 11 (0.00%) 0	2 / 27 (7.41%) 2
Nasal congestion			

subjects affected / exposed	1 / 36 (2.78%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Sputum increased			
subjects affected / exposed	0 / 36 (0.00%)	1 / 11 (9.09%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	3 / 27 (11.11%)
occurrences (all)	0	0	3
Dyspnoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Skin disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 36 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 36 (8.33%)	0 / 11 (0.00%)	3 / 27 (11.11%)
occurrences (all)	3	0	3
Pseudomonas infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 11 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 11 (9.09%)	0 / 27 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part B: VX-371 + Ivacaftor	Part B: Placebo + Ivacaftor	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	9 / 12 (75.00%)	
Investigations			
Haemophilus test positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Moraxella test positive			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Amylase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Forced expiratory volume decreased			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 12 (8.33%) 1	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 12 (0.00%) 0	
Streptococcus test positive subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 12 (8.33%) 1	
Weight decreased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 12 (0.00%) 0	
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 12 (0.00%) 0	
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 12 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	3 / 12 (25.00%) 3	
General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 12 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 12 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 12 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 12 (8.33%) 1	

Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			

subjects affected / exposed	2 / 7 (28.57%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Sputum increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Skin disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Rash pruritic subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 12 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 12 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pseudomonas infection subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2016	- Moved PCD genotype collection from Day 1 to Screening Visit - Added new exclusion criterion to exclude pregnant and/or nursing females
06 June 2016	- Modified contraception language
15 August 2016	- Modified contraception language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported