



Clinical trial results:

A Pilot Study Testing the Effect of Ivacaftor on Lung Function in Subjects With Cystic Fibrosis, Residual CFTR Function, and FEV1 40% Predicted

Summary

EudraCT number	2017-000673-37
Trial protocol	Outside EU/EEA
Global end of trial date	03 April 2014

Results information

Result version number	v1 (current)
This version publication date	08 June 2017
First version publication date	08 June 2017

Trial information

Trial identification

Sponsor protocol code	VX12-770-113
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01685801
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 022101862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of ivacaftor on lung function in subjects aged 12 years and older with cystic fibrosis (CF) who have phenotypic or molecular evidence of residual cystic fibrosis transmembrane conductance regulator (CFTR) function.

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	11 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

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)	1
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 24 subjects were enrolled at a single site in United States.

Period 1

Period 1 title	Cycle 1 Period 1 (2 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 1

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during first intervention period.

Arm type	Experimental
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:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 1 Period 1.

Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 1
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during first intervention period.

Arm type	Experimental
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:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 1 Period 1.

Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 1
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received

Placebo matched to Ivacaftor during first intervention period.

Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 1 Period 1.	
Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 1

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during first intervention period.

Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 1 Period 1.

Number of subjects in period 1	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 1	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 1	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 1
Started	5	6	7
Completed	5	6	7

Number of subjects in period 1	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 1
Started	6
Completed	6

Period 2

Period 2 title	Cycle 1 Period 2 (2 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
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Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 2
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during second intervention period.

Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 1 Period 2.

Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 2
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during second intervention period.

Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 1 Period 2.

Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 2
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during second intervention period.

Arm type	Experimental
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:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 1 Period 2.

Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 2
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during second intervention period.

Arm type	Experimental
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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:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 1 Period 2.

Number of subjects in period 2	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 2	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 2	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 2
Started	5	6	7
Completed	5	6	7
Not completed	0	0	0
Adverse Event	-	-	-

Number of subjects in period 2	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 2
Started	6
Completed	5
Not completed	1
Adverse Event	1

Period 3

Period 3 title	Washout Period 1 (4 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Washout Period

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Washout Period

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label

Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Washout Period
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Washout Period
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Number of subjects in period 3	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Washout Period	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Washout Period	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Washout Period
Started	5	6	7
Completed	5	6	7

Number of subjects in period 3	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Washout Period
Started	5
Completed	5

Period 4

Period 4 title	Cycle 2 Period 1 (2 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
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Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 3
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during third intervention period.	
Arm type	Experimental
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:	
Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 2 Period 1.	
Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 3
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during third intervention period.	
Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 2 Period 1.	
Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 3
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Ivacaftor during third intervention period.	
Arm type	Experimental
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:	
Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 2 Period 1.	
Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 3
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Placebo matched Ivacaftor during third intervention period.	
Arm type	Placebo

Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 2 Period 1.

Number of subjects in period 4	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 3	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 3	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 3
Started	5	6	7
Completed	5	6	7

Number of subjects in period 4	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 3
Started	5
Completed	5

Period 5

Period 5 title	Cycle 2 Period 2 (2 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 4

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Placebo matched to Ivacaftor during fourth intervention period.

Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 2 Period 2.

Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 4
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during fourth intervention period.	
Arm type	Experimental
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:	
Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 2 Period 2.	
Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 4
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Placebo matched to Ivacaftor during fourth intervention period.	
Arm type	Placebo
Investigational medicinal product name	Placebo-matched-to-ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during Cycle 2 Period 2.	
Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 4
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during fourth intervention period.	
Arm type	Experimental
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:	
Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during Cycle 2 Period 2.	

Number of subjects in period 5	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 4	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 4	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 4
Started	5	6	7
Completed	5	5	7
Not completed	0	1	0
Non-compliance with Study Drug	-	1	-

Number of subjects in period 5	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 4
Started	5
Completed	4
Not completed	1
Non-compliance with Study Drug	1

Period 6

Period 6 title	Washout Period 2 (4 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Washout Period

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Washout Period
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Washout Period
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Washout Period
Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 6	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Washout Period	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Washout Period	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Washout Period
Started	5	5	7
Completed	5	5	7

Number of subjects in period 6	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Washout Period
Started	4
Completed	4

Period 7	
Period 7 title	Open-label Period (8 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP)

Arm description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.	
Arm type	Experimental
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:	
Ivacaftor 150 mg tablet orally every 12 hours for 8 weeks in open-label period.	
Arm title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI)

Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	Experimental
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:

Ivacaftor 150 mg tablet orally every 12 hours for 8 weeks in open-label period.

Arm title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP)
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	Experimental
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:

Ivacaftor 150 mg tablet orally every 12 hours for 8 weeks in open-label period.

Arm title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI)
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Arm description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Arm type	Experimental
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:

Ivacaftor 150 mg tablet orally every 12 hours for 8 weeks in open-label period.

Number of subjects in period 7	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP)	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI)	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP)
Started	5	5	7
Completed	5	5	7

Number of subjects in period 7	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI)
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Started	4
Completed	4

Baseline characteristics

Reporting groups

Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 1
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during first intervention period.

Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 1
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during first intervention period.

Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 1
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during first intervention period.

Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 1
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during first intervention period.

Reporting group values	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 1	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 1	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 1
Number of subjects	5	6	7
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	44.8 ± 8.04	29.7 ± 11.66	41.4 ± 13.96
Gender categorical Units: Subjects			
Female	3	4	3
Male	2	2	4
Genotype			
All subjects were tested for CFTR genotype. Subjects with a documented medical history of either a residual function or a messenger ribonucleic acid (mRNA) splice site (Class V) CFTR mutation were reported.			
Units: Subjects			
mRNA Splice Site (Class V) Mutations	3	3	2

Residual Function Mutations	2	3	5
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Reporting group values	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 1	Total	
Number of subjects	6	24	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	33.8 ± 17.26	-	
Gender categorical Units: Subjects			
Female	2	12	
Male	4	12	
Genotype			
All subjects were tested for CFTR genotype. Subjects with a documented medical history of either a residual function or a messenger ribonucleic acid (mRNA) splice site (Class V) CFTR mutation were reported.			
Units: Subjects			
mRNA Splice Site (Class V) Mutations	2	10	
Residual Function Mutations	4	14	

End points

End points reporting groups

Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 1
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during first intervention period.	
Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 1
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during first intervention period.	
Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 1
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during first intervention period.	
Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 1
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during first intervention period.	
Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 2
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during second intervention period.	
Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 2
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during second intervention period.	
Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 2
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during second intervention period.	
Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 2
Reporting group description: During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during second intervention period.	

Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Washout Period
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.	
Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Washout Period
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.	
Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Washout Period
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.	
Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Washout Period
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.	
Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 3
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during third intervention period.	
Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 3
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Placebo matched to Ivacaftor during third intervention period.	
Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 3
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Ivacaftor during third intervention period.	
Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 3
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Placebo matched Ivacaftor during third intervention period.	
Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Intervention 4
Reporting group description:	
During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Placebo matched to Ivacaftor during fourth intervention period.	
Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Intervention 4

Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during fourth intervention period.

Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Intervention 4
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received Ivacaftor. Subjects received Placebo matched to Ivacaftor during fourth intervention period.

Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Intervention 4
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor. Subjects received Ivacaftor during fourth intervention period.

Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP) - Washout Period
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI) - Washout Period
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP) - Washout Period
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI) - Washout Period
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Ivacaftor, Placebo, Ivacaftor, Placebo (IPIP)
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Ivacaftor, Placebo, Placebo, Ivacaftor (IPPI)
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Placebo, Ivacaftor, Ivacaftor, Placebo (PIIP)
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label

Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Reporting group title	Placebo, Ivacaftor, Placebo, Ivacaftor (PIPI)
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Reporting group description:

During the Crossover Period, study drug was administered in 2-week alternating cycles with a minimum of 4-week washout period between Cycle 1 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and Cycle 2 [(Period 1 - Day 1 to 14) (Period 2 - Day 15 to 29)] and between Cycle 2 and the Open-label Period (Day 1 to 57). During the Open-label Period, all subjects received ivacaftor.

Subject analysis set title	Cycle 1: Placebo
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Subject analysis set type	Full analysis
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Subject analysis set description:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during either in period 1 or 2 of Cycle 1.

Subject analysis set title	Cycle 1: Ivacaftor
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Subject analysis set type	Full analysis
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Subject analysis set description:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during either in period 1 or 2 of Cycle 1.

Subject analysis set title	Cycle 2: Placebo
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Subject analysis set type	Full analysis
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Subject analysis set description:

Placebo-matched-to-ivacaftor tablet orally every 12 hours for 2 weeks during either in period 1 or 2 of Cycle 2.

Subject analysis set title	Cycle 2: Ivacaftor
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Subject analysis set type	Full analysis
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Subject analysis set description:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks during either in period 1 or 2 of Cycle 2.

Subject analysis set title	Open-Label Period: Ivacaftor
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Subject analysis set type	Full analysis
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Subject analysis set description:

Ivacaftor 150 mg tablet orally every 12 hours for 8 weeks during the open-label period after washout period 2.

Subject analysis set title	Crossover Double-blind Period: Placebo
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Subject analysis set type	Full analysis
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Subject analysis set description:

Placebo matched to ivacaftor tablet orally every 12 hours for 2 weeks either during the double blind period 1 or 2 of cycle 1 and cycle 2.

Subject analysis set title	Crossover Double-blind Period: Ivacaftor
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Subject analysis set type	Full analysis
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Subject analysis set description:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks either during the double blind period 1 or 2 of cycle 1 and cycle 2.

Primary: Cycle 1 and Cycle 2: Absolute Change From Cycle Baseline In Percent Predicted Forced Expiratory Volume In 1 Second (FEV1) After 2 Weeks of Treatment

End point title	Cycle 1 and Cycle 2: Absolute Change From Cycle Baseline In Percent Predicted Forced Expiratory Volume In 1 Second (FEV1) After 2 Weeks of Treatment
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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. Hankinson and Wang standards were used to calculate percent predicted FEV1 (for age, gender, and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 12 to 17 years and for female subjects aged 12 to 15 years. Data was to be reported for each cycle (Cycle 1 and Cycle 2) and as per drug treatment, for overall subjects and as per genotype (residual function mutation and mRNA splice site mutation). Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). Here, number of subjects analyzed signifies subject evaluable for this endpoint and "n" signifies subject who were evaluable for the specified category in each arm, respectively.

End point type	Primary
End point timeframe:	
Cycle 1 baseline, Cycle 1 Day 15 (for Cycle 1 reporting arms); Cycle 2 baseline, Cycle 2 Day 15 (for Cycle 2 reporting arms)	

End point values	Cycle 1: Placebo	Cycle 1: Ivacaftor	Cycle 2: Placebo	Cycle 2: Ivacaftor
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	24	23	23
Units: Percent predicted of FEV1				
arithmetic mean (standard deviation)				
Overall (n=24, 24, 23, 23)	0.5828 (± 3.67326)	2.0898 (± 4.63833)	0.8495 (± 4.20641)	3.6868 (± 6.13466)
mRNA Splice Site(ClassV)Mutations (n=10, 10, 9, 9)	-0.571 (± 3.39739)	0.8196 (± 5.09161)	1.7132 (± 3.80933)	2.064 (± 3.55493)
Residual Function Mutations (n=14, 14, 14, 14)	1.4069 (± 3.75842)	2.9971 (± 4.24124)	0.2942 (± 4.49056)	4.73 (± 7.27436)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
This statistical analysis is for "Overall" category. The posterior distribution of overall treatment difference was obtained using the Bayesian hierarchical model and 95% credible interval of the treatment effect (posterior mean) was calculated.	
Comparison groups	Cycle 1: Placebo v Cycle 1: Ivacaftor v Cycle 2: Placebo v Cycle 2: Ivacaftor
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Posterior Mean
Point estimate	2.251
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.383
upper limit	4.144
Variability estimate	Standard deviation
Dispersion value	0.961

Secondary: Cycle 1 and Cycle 2: Absolute Change From Cycle Baseline In Lung Clearance Index (LCI) After 2 Weeks of Treatment

End point title	Cycle 1 and Cycle 2: Absolute Change From Cycle Baseline In Lung Clearance Index (LCI) After 2 Weeks of Treatment
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End point description:

LCI is a measure of ventilation inhomogeneity that is derived from a multiple-breath washout test. The LCI was calculated as the number of lung volume turnovers (cumulative expired volume divided by the functional residual capacity [FRC]) required to reduce end-tidal concentration of an inert gas to 1/40th

of the starting value. Data was to be reported for each cycle (Cycle 1 and Cycle 2) and as per drug treatment. Data was to be reported for each cycle (Cycle 1 and Cycle 2) and as per drug treatment, for overall subjects and as per genotype (residual function mutation and mRNA splice site mutation). FAS population. Here, "number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies subjects who were evaluable for the specified category in each arm, respectively.

End point type	Secondary
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End point timeframe:

Cycle 1 baseline, Cycle 1 Day 15 (for Cycle 1 reporting arms); Cycle 2 baseline, Cycle 2 Day 15 (for Cycle 2 reporting arms)

End point values	Cycle 1: Placebo	Cycle 1: Ivacaftor	Cycle 2: Placebo	Cycle 2: Ivacaftor
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	24	23	22
Units: Ratio				
arithmetic mean (standard deviation)				
Overall (n=23, 24, 23, 22)	0.4596 ($\pm$ 1.97774)	0.2822 ($\pm$ 3.54741)	0.4111 ($\pm$ 2.3992)	0.077 ($\pm$ 1.98188)
mRNA Splice Site(ClassV)Mutations (n=10, 10, 9, 9)	0.4321 ($\pm$ 1.9714)	-0.5306 ($\pm$ 1.91374)	1.0568 ($\pm$ 2.12093)	-0.3136 ($\pm$ 1.89562)
Residual Function Mutations (n=13, 14, 14, 13)	0.4808 ($\pm$ 2.06279)	0.8628 ($\pm$ 4.34252)	-0.0039 ($\pm$ 2.54929)	0.3475 ($\pm$ 2.0699)

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Period: Absolute Change From Open-label Baseline In Percent Predicted Forced Expiratory Volume In 1 Second (FEV1) at Day 57

End point title	Open-label Period: Absolute Change From Open-label Baseline In Percent Predicted Forced Expiratory Volume In 1 Second (FEV1) at Day 57
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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. Hankinson and Wang standards were used to calculate percent predicted FEV1 (for age, gender, and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 12 to 17 years and for female subjects aged 12 to 15 years. Data was to be reported for overall subjects and as per genotype (residual function mutation and mRNA splice site mutation). FAS population. Here, "number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary
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End point timeframe:

Open-label Baseline, Open-label Day 57

End point values	Open-Label Period: Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Percent predicted of FEV1				
arithmetic mean (standard deviation)				
Overall (n=21)	4.6815 ($\pm$ 4.17934)			
mRNA Splice Site(ClassV)Mutations (n=9)	4.3072 ($\pm$ 2.93624)			
Residual Function Mutations (n=12)	4.9622 ($\pm$ 5.02864)			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Period: Absolute Change From Open-label Baseline In Lung Clearance Index (LCI) at Day 57

End point title	Open-label Period: Absolute Change From Open-label Baseline In Lung Clearance Index (LCI) at Day 57
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End point description:

LCI is a measure of ventilation inhomogeneity that is derived from a multiple-breath washout test. The LCI was calculated as the number of lung volume turnovers (cumulative expired volume divided by the functional residual capacity [FRC]) required to reduce end-tidal concentration of an inert gas to 1/40th of the starting value. Data was to be reported for overall subjects and as per genotype (residual function mutation and mRNA splice site mutation). FAS population. Here, "number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary
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End point timeframe:

Open-label Baseline, Open-label Day 57

End point values	Open-Label Period: Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Ratio				
arithmetic mean (standard deviation)				
Overall (n=21)	-1.5687 ($\pm$ 2.27137)			
mRNA Splice Site(ClassV)Mutations (n=9)	-1.3459 ($\pm$ 2.88447)			
Residual Function Mutations (n=12)	-1.7358 ($\pm$ 1.80502)			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Period: Absolute Change From Study Baseline In Sweat Chloride at Day 57

End point title	Open-label Period: Absolute Change From Study Baseline In Sweat Chloride at Day 57
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End point description:

Sweat samples were collected using an approved Macroduct (Wescor, Logan, Utah) collection device. A volume of greater than or equal to ($\geq$) 15 microliter was required for determination of sweat chloride. Data was to be reported for overall subjects and as per genotype (residual function mutation and mRNA splice site mutation). FAS population. Here, "number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary
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End point timeframe:

Study Baseline, Open-label Day 57

End point values	Open-Label Period: Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Overall (n=19)	-15.74 ($\pm$ 14.781)			
mRNA Splice Site(ClassV)Mutations (n=8)	-14.13 ($\pm$ 8.254)			
Residual Function Mutations (n=11)	-16.91 ($\pm$ 18.493)			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-label Period: Absolute Change From Open-label Baseline In Weight at Day 57

End point title	Open-label Period: Absolute Change From Open-label Baseline In Weight at Day 57
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End point description:

Data was to be reported for overall subjects and as per genotype (residual function mutation and mRNA splice site mutation). FAS population. Here, "number of subjects analyzed" signifies subjects evaluable for this endpoint and "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary
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End point timeframe:

Open-label Baseline, Open-label Day 57

End point values	Open-Label Period: Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Kilograms (kg)				
arithmetic mean (standard deviation)				
Overall (n=21)	1.77 (± 1.906)			
mRNA Splice Site(ClassV)Mutations (n=9)	2.32 (± 2.111)			
Residual Function Mutations (n=12)	1.35 (± 1.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)
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End point description:

AEs that started(or increased severity)from first dose of study drug to completion of Follow-up were TEAEs, with exception that if AE started during Washout Period & beyond 14 days from last dose date of preceding cycle, AE was "Washout Period" AE & not TEAE. TEAE was attributed to treatment in which it started/ to treatment in second cycling period of previous Crossover Period if it started during Washout Period. SAE:medical event/condition, which falls into any of these categories, regardless of relationship to study drug: death, life threatening adverse experience, in-patient hospitalization/prolongation of hospitalization, persistent/significant disability/incapacity, congenital anomaly/birth defect, important medical event. Data was to be reported by drug treatment for double-blind crossover period(Cycle 1 up to Washout Period 2)& open-label period. Safety set:all subjects who received at least 1 dose of study drug. Number of subjects analyzed=subject evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

From first dose of study drug through completion of follow-up visit (up to 26 weeks)

End point values	Open-Label Period: Ivacaftor	Crossover Double-blind Period: Placebo	Crossover Double-blind Period: Ivacaftor	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21	24	24	
Units: Subjects				
AEs	20	17	18	
SAEs	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through completion of follow-up visit (up to 26 weeks)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Crossover Double-blind Period: Placebo
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Reporting group description:

Placebo matched to ivacaftor tablet orally every 12 hours for 2 weeks either during the double blind period 1 or 2 of cycle 1 and cycle 2.

Reporting group title	Crossover Double-blind Period: Ivacaftor
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Reporting group description:

Ivacaftor 150 mg tablet orally every 12 hours for 2 weeks either during the double blind period 1 or 2 of cycle 1 and cycle 2.

Reporting group title	Open-label Period: Ivacaftor
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Reporting group description:

Ivacaftor 150 mg tablet orally every 12 hours for 8 weeks during the open-label period after washout period 2.

Serious adverse events	Crossover Double-blind Period: Placebo	Crossover Double-blind Period: Ivacaftor	Open-label Period: Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Crossover Double-blind Period: Placebo	Crossover Double-blind Period: Ivacaftor	Open-label Period: Ivacaftor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 24 (70.83%)	18 / 24 (75.00%)	20 / 21 (95.24%)

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	0 / 24 (0.00%)	4 / 21 (19.05%)
occurrences (all)	3	0	5
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	3 / 24 (12.50%)	0 / 21 (0.00%)
occurrences (all)	1	3	0
Chest discomfort			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 24 (25.00%)	1 / 24 (4.17%)	7 / 21 (33.33%)
occurrences (all)	7	1	7
Haemoptysis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Oropharyngeal pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Paranasal sinus hypersecretion			

subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Sputum increased			
subjects affected / exposed	7 / 24 (29.17%)	1 / 24 (4.17%)	2 / 21 (9.52%)
occurrences (all)	7	1	2
Respiration abnormal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Sinus congestion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Sneezing			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Throat irritation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Wheezing			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Dyspnoea			
subjects affected / exposed	4 / 24 (16.67%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	4	0	1
Nasal congestion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Upper-airway cough syndrome			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Dysphonia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 24 (0.00%) 0	0 / 21 (0.00%) 0
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 24 (0.00%) 0	0 / 21 (0.00%) 0
Respiratory tract irritation subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 24 (0.00%) 0	0 / 21 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Investigations Liver function test abnormal subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Excoriation subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Wrist fracture subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 24 (0.00%) 0	0 / 21 (0.00%) 0
Cardiac disorders Cardiac flutter subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Nervous system disorders Sinus headache			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 24 (8.33%) 2	2 / 21 (9.52%) 2
Headache subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 24 (8.33%) 2	1 / 21 (4.76%) 1
Dizziness subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 24 (0.00%) 0	0 / 21 (0.00%) 0
Skin and subcutaneous tissue disorders Heat rash subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0
Urticaria			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Intervertebral disc protrusion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal discomfort			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Osteopenia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	5 / 24 (20.83%)	4 / 21 (19.05%)
occurrences (all)	0	5	4
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	3 / 24 (12.50%)	1 / 24 (4.17%)	2 / 21 (9.52%)
occurrences (all)	4	1	2
Acute sinusitis			

subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Incision site infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Oral viral infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	3 / 24 (12.50%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2012	- Secondary efficacy endpoint Cystic Fibrosis Questionnaire Revised (CFQ-R) was removed; - Assessment for alanine aminotransferase and aspartate aminotransferase was added; - Pulse oximetry assessment changed to twice daily; - Prior ivacaftor use was added as an exclusion criterion; - The analysis of the primary variable was updated.
02 April 2013	- Subjects who completed this study were offered to enroll in Study VX12-770-112 (2012-000389-39); The number of subjects to be enrolled was increased
29 July 2013	- Responder criteria for participation in Study VX12-770-112 were incorporated and relative change in percent predicted FEV1 was amended to absolute change to facilitate comparison of data among ivacaftor clinical studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported