



Clinical trial results:

A Phase 3, Two-Arm, Rollover Study to Evaluate the Safety of Long-Term Ivacaftor Treatment in Subjects 6 Years of Age and Older with Cystic

Fibrosis and a Non-G551D CFTR Mutation

Summary

EudraCT number	2012-000389-39
Trial protocol	GB BE
Global end of trial date	18 April 2016

Results information

Result version number	v1 (current)
This version publication date	02 November 2016
First version publication date	02 November 2016

Trial information

Trial identification

Sponsor protocol code	VX12-770-112
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01707290
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, 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)	Yes
EMA paediatric investigation plan number(s)	EMA-000335-PIP01-08
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	30 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of long-term ivacaftor treatment in subjects with cystic fibrosis (CF).

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	13 February 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 93
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	125
EEA total number of subjects	32

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)	22
Adolescents (12-17 years)	12
Adults (18-64 years)	89

From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of 2 arms: Ivacaftor arm and Observational arm. The Ivacaftor arm enrolled subjects from Study VX11-770-110 (2012-000387-19), Study VX12-770-111 (2012-000388-26) and Study VX12-770-113. The Observational arm enrolled subjects from Study VX11-770-110 (2012-000387-19) and Study VX12-770-111 (2012-000388-26).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivacaftor arm

Arm description:

Subjects who received Ivacaftor 150 milligram (mg) tablet and/or Placebo matched to ivacaftor tablet every 12 hours (q12h) in the previous study VX11-770-110 (Study 110; 2012-000387-19), VX12-770-111 (Study 111; 2012-000388-26) or VX12-770-113 (Study 113); received Ivacaftor 150 mg tablet q12h in this VX12-770-112 (Study 112; 2012-000389-39) up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor 150 mg tablet q12h for 104 weeks.

Arm title	Observational arm
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Arm description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110 or Study 111, were observed (did not receive study drug) in this Study 112 for up to 2 years.

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

Number of subjects in period 1	Ivacaftor arm	Observational arm
Started	121	4
Completed	35	3
Not completed	86	1
Commercial drug available	60	1
Physician decision	1	-
Adverse Event (AE)	1	-

Other unspecified	17	-
Withdrawal of Consent (Not Due to AE)	4	-
Lost to follow-up	3	-

Baseline characteristics

Reporting groups

Reporting group title	Ivacaftor arm
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Reporting group description:

Subjects who received Ivacaftor 150 milligram (mg) tablet and/or Placebo matched to ivacaftor tablet every 12 hours (q12h) in the previous study VX11-770-110 (Study 110; 2012-000387-19), VX12-770-111 (Study 111; 2012-000388-26) or VX12-770-113 (Study 113); received Ivacaftor 150 mg tablet q12h in this VX12-770-112 (Study 112; 2012-000389-39) up to 104 weeks.

Reporting group title	Observational arm
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Reporting group description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110 or Study 111, were observed (did not receive study drug) in this Study 112 for up to 2 years.

Reporting group values	Ivacaftor arm	Observational arm	Total
Number of subjects	121	4	125
Age categorical Units: Subjects			
6 to 11 years	21	1	22
12 to 17 years	11	1	12
18 years and over	89	2	91
Gender categorical Units: Subjects			
Female	61	3	64
Male	60	1	61

End points

End points reporting groups

Reporting group title	Ivacaftor arm
Reporting group description: Subjects who received Ivacaftor 150 milligram (mg) tablet and/or Placebo matched to ivacaftor tablet every 12 hours (q12h) in the previous study VX11-770-110 (Study 110; 2012-000387-19), VX12-770-111 (Study 111; 2012-000388-26) or VX12-770-113 (Study 113); received Ivacaftor 150 mg tablet q12h in this VX12-770-112 (Study 112; 2012-000389-39) up to 104 weeks.	
Reporting group title	Observational arm
Reporting group description: Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110 or Study 111, were observed (did not receive study drug) in this Study 112 for up to 2 years.	
Subject analysis set title	Ivacaftor arm: Study 110
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110; received Ivacaftor 150 mg tablet q12h in this Study 112 up to 104 weeks.	
Subject analysis set title	Ivacaftor arm: Study 111
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 111; received Ivacaftor 150 mg tablet q12h in this Study 112 up to 104 weeks.	
Subject analysis set title	Ivacaftor arm: Study 113
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 113; received Ivacaftor 150 mg tablet q12h in this Study 112 up to 104 weeks.	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs) in Ivacaftor arm

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs) in Ivacaftor arm ^{[1][2]}
End point description: AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after informed consent form is signed. AE includes serious as well as non-serious AEs. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, In-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. TEAEs were defined as adverse events with start date or increased severity on and after the first dose of study drug through Week 108. Safety Set included all subjects who received at least 1 dose of study drug (ivacaftor).	
End point type	Primary
End point timeframe: Day 1 up to Week 108	

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 reported, inferential statistics were not planned for primary endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only arms which are applicable to the endpoint are reported.

End point values	Ivacaftor arm			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: subjects				
number (not applicable)				
Subjects with AEs	117			
Subjects with SAEs	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96, and 104

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96, and 104
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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 6 to 17 years and for female subjects aged 6 to 15 years. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). Full Analysis Set (FAS) included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 (Study 112)

End point values	Ivacaftor arm: Study 110	Ivacaftor arm: Study 111	Ivacaftor arm: Study 113	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	65	35	21	
Units: Percent predicted of FEV1				
arithmetic mean (standard deviation)				
Baseline (n= 65, 35, 21)	71.8 (± 20.4)	78.3 (± 21.1)	62.8 (± 22.2)	
Change at Week 2 (n= 65, 35, 21)	3.8 (± 8)	4.4 (± 7.7)	4 (± 7.2)	
Change at Week 12 (n=63, 33, 21)	5.4 (± 8.9)	5.5 (± 8.3)	4.9 (± 6.7)	
Change at Week 24 (n= 62, 34, 21)	4.5 (± 8.4)	7.1 (± 8.3)	4.6 (± 8.5)	
Change at Week 36 (n= 60, 29, 20)	4.4 (± 7.1)	7.5 (± 8.2)	4.9 (± 8.2)	
Change at Week 48 (n= 58, 19, 20)	4.4 (± 7.5)	6.4 (± 10.7)	4.9 (± 9)	
Change at Week 60 (n= 58, 16, 20)	4.5 (± 8.4)	8.2 (± 8.3)	4.5 (± 8.8)	
Change at Week 72 (n= 50, 13, 18)	3.6 (± 8.9)	7.8 (± 9.2)	5.9 (± 9.2)	
Change at Week 84 (n= 40, 11, 16)	5.4 (± 13.5)	7.7 (± 7.6)	4.8 (± 7.2)	
Change at Week 96 (n= 28, 9, 15)	4.1 (± 14.6)	9.9 (± 6.4)	5.9 (± 8.1)	
Change at Week 104 (n= 20, 9, 12)	4.6 (± 13.2)	4.9 (± 5.8)	6.3 (± 10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Body Mass Index (BMI) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104

End point title	Absolute Change From Baseline in Body Mass Index (BMI) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104
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End point description:

BMI was defined as weight in kg divided by height in m². Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). FAS included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 (Study 112)

End point values	Ivacaftor arm: Study 110	Ivacaftor arm: Study 111	Ivacaftor arm: Study 113	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	65	35	21	
Units: kilogram per square meter (kg/m ²)				
arithmetic mean (standard deviation)				
Baseline (n= 65, 35, 21)	23.75 (± 5.63)	23.15 (± 5.28)	24.81 (± 5.76)	
Change at Week 2 (n= 65, 35, 21)	0.06 (± 0.43)	0.16 (± 0.47)	0.07 (± 0.43)	
Change at Week 12 (n= 64, 35, 21)	0.32 (± 0.59)	0.39 (± 0.62)	0.22 (± 0.6)	
Change at Week 24 (n= 62, 35, 21)	0.43 (± 0.92)	0.65 (± 0.96)	0.17 (± 0.91)	
Change at Week 36 (n= 60, 29, 20)	0.62 (± 1.04)	0.64 (± 1.07)	0.02 (± 1.27)	
Change at Week 48 (n=59, 19, 20)	0.54 (± 1.39)	0.58 (± 1.22)	0.28 (± 1.26)	
Change at Week 60 (n= 58, 16, 20)	0.72 (± 1.32)	0.25 (± 1.09)	0.38 (± 1.22)	
Change at Week 72 (n= 51, 13, 17)	1.05 (± 1.73)	0.45 (± 1.34)	0.22 (± 1.22)	
Change at Week 84 (n= 40, 11, 16)	0.72 (± 1.51)	0.33 (± 1.42)	0.23 (± 0.92)	
Change at Week 96 (n= 28, 9, 16)	0.49 (± 1.44)	0.1 (± 1.49)	0.52 (± 1.28)	
Change at Week 104 (n= 20, 9, 12)	0.42 (± 1.49)	0.16 (± 1.37)	0.88 (± 1.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Sweat Chloride at Week 2, 24, 48 and 104

End point title	Absolute Change From Baseline in Sweat Chloride at Week 2, 24, 48 and 104
End point description: Sweat samples were collected using an approved collection device. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). FAS included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "Number of subjects analysed" signifies those subjects who were evaluable for this outcome and "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm respectively.	
End point type	Secondary
End point timeframe: Baseline, Week 2, 24, 48 and 104 (Study 112)	

End point values	Ivacaftor arm: Study 110	Ivacaftor arm: Study 111	Ivacaftor arm: Study 113	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	59	33	21	
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Baseline (n=59, 33, 21)	60.9 (± 19.4)	80.2 (± 22.8)	55.7 (± 22.2)	
Change at Week 2 (n=59, 31, 21)	-19.3 (± 10.7)	-38.4 (± 27.5)	-4.5 (± 10.9)	
Change at Week 24 (n=56, 33, 20)	-13 (± 18.4)	-39.2 (± 27)	1.1 (± 15.8)	
Change at Week 48 (n=50, 19, 19)	-13.5 (± 16.2)	-40.6 (± 26.1)	-1.9 (± 17.8)	
Change at Week 104 (n=15, 9, 11)	-13.7 (± 22.9)	-32.9 (± 26.8)	5.4 (± 18.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Respiratory Domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104

End point title	Absolute Change From Baseline in Respiratory Domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104
End point description: The CFQ-R is a validated subject reported outcome measuring health related quality of life for subjects with CF. Respiratory domain assessed respiratory symptoms (for example, coughing, congestion, wheezing), score range: 0-100; higher scores indicating fewer symptoms and better health related quality of life. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). FAS included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm respectively.	
End point type	Secondary
End point timeframe: Baseline, Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 (Study 112)	

End point values	Ivacaftor arm: Study 110	Ivacaftor arm: Study 111	Ivacaftor arm: Study 113	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	65	35	21	
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 65, 35, 21)	68.6 (± 21.6)	72.4 (± 20.3)	65.9 (± 18.8)	
Change at Week 2 (n= 65, 35, 21)	5.5 (± 17.9)	4.5 (± 17.5)	13.2 (± 16.2)	
Change at Week 12 (n= 64, 35, 21)	11.6 (± 18)	5.7 (± 18.5)	13.5 (± 20)	
Change at Week 24 (n= 62, 35, 21)	6.7 (± 19)	3.4 (± 18.7)	8.5 (± 14.9)	
Change at Week 36 (n=60, 29, 20)	12.1 (± 19.3)	5.7 (± 13.8)	7.9 (± 20.5)	
Change at Week 48 (n= 59, 19, 20)	9.5 (± 17.6)	4.4 (± 13.2)	11.4 (± 15.7)	
Change at Week 60 (n= 57, 15, 20)	7.1 (± 18.6)	4.4 (± 10.9)	8.6 (± 19.3)	
Change at Week 72 (n= 51, 13, 18)	10.4 (± 22.2)	5.6 (± 11.8)	8.6 (± 19)	
Change at Week 84 (n= 40, 11, 16)	10.5 (± 19.5)	8.8 (± 14.1)	4.9 (± 14.6)	
Change at Week 96 (n= 28, 9, 16)	8.8 (± 21.1)	0 (± 9.5)	9.4 (± 14.7)	
Change at Week 104 (n= 20, 9, 12)	9.2 (± 14)	1.9 (± 8.8)	19.9 (± 16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Pulmonary Exacerbations Events

End point title	Number of Pulmonary Exacerbations Events
End point description:	
Pulmonary exacerbation events include those events which require treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. The number of events were reported. FAS included all subjects who received at least 1 dose of study drug (ivacaftor).	
End point type	Secondary
End point timeframe:	
Through Week 104	

End point values	Ivacaftor arm: Study 110	Ivacaftor arm: Study 111	Ivacaftor arm: Study 113	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	65	35	21	
Units: pulmonary exacerbation events				
number (not applicable)	47	30	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With SAEs in Observational arm

End point title	Number of Subjects With SAEs in Observational arm ^[3]
End point description:	
SAE was defined as a medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, In-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. Analysis population included all subjects who were included in the observational arm.	
End point type	Secondary
End point timeframe:	
up to 2 years	

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only arms which are applicable to the endpoint are reported.

End point values	Observational arm			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: subjects				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 108 for Ivacaftor arm; up to 2 years for Observational arm

Adverse event reporting additional description:

Non-SAEs were not collected for Observational arm. Only SAEs were planned to be collected for the Observational arm.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Ivacaftor arm
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Reporting group description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous study 110 (2012-000387-19) or study 111 (2012-000388-26) or study 113, received Ivacaftor 150 mg tablet q12h in this study 112 (2012-000389-39) up to 104 weeks.

Reporting group title	Observational arm
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Reporting group description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous study 110 (2012-000387-19) or study 111 (2012-000388-26), were observed (did not receive study drug) in this study 112 (2012-000389-39) for up to 2 years.

Serious adverse events	Ivacaftor arm	Observational arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 121 (22.31%)	1 / 4 (25.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Influenza A virus test positive			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy acute			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	21 / 121 (17.36%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	1 / 34	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis bacterial			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ivacaftor arm	Observational arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	117 / 121 (96.69%)	0 / 4 (0.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Thyroid neoplasm			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hot flush			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 121 (14.05%)	0 / 4 (0.00%)	
occurrences (all)	25	0	
Fatigue			
subjects affected / exposed	12 / 121 (9.92%)	0 / 4 (0.00%)	
occurrences (all)	15	0	
Chest pain			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	

Influenza like illness			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Chills			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Feeling of body temperature change			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Asthenia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Device leakage			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Implant site rash			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vaccination site pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Allergy to arthropod bite			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Breast pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Menorrhagia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Testicular torsion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal discomfort			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pruritus			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 121 (33.88%)	0 / 4 (0.00%)	
occurrences (all)	81	0	
Sputum increased			
subjects affected / exposed	22 / 121 (18.18%)	0 / 4 (0.00%)	
occurrences (all)	27	0	
Sinus congestion			

subjects affected / exposed	22 / 121 (18.18%)	0 / 4 (0.00%)
occurrences (all)	34	0
Oropharyngeal pain		
subjects affected / exposed	18 / 121 (14.88%)	0 / 4 (0.00%)
occurrences (all)	24	0
Nasal congestion		
subjects affected / exposed	17 / 121 (14.05%)	0 / 4 (0.00%)
occurrences (all)	20	0
Dyspnoea		
subjects affected / exposed	12 / 121 (9.92%)	0 / 4 (0.00%)
occurrences (all)	14	0
Respiratory tract congestion		
subjects affected / exposed	9 / 121 (7.44%)	0 / 4 (0.00%)
occurrences (all)	12	0
Haemoptysis		
subjects affected / exposed	12 / 121 (9.92%)	0 / 4 (0.00%)
occurrences (all)	25	0
Wheezing		
subjects affected / exposed	9 / 121 (7.44%)	0 / 4 (0.00%)
occurrences (all)	10	0
Rales		
subjects affected / exposed	7 / 121 (5.79%)	0 / 4 (0.00%)
occurrences (all)	8	0
Rhinorrhoea		
subjects affected / exposed	6 / 121 (4.96%)	0 / 4 (0.00%)
occurrences (all)	6	0
Paranasal sinus hypersecretion		
subjects affected / exposed	5 / 121 (4.13%)	0 / 4 (0.00%)
occurrences (all)	6	0
Pleuritic pain		
subjects affected / exposed	5 / 121 (4.13%)	0 / 4 (0.00%)
occurrences (all)	9	0
Respiration abnormal		
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)
occurrences (all)	7	0
Nasal polyps		

subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	5	0
Throat irritation		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	3	0
Dysphonia		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Nasal mucosal disorder		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Productive cough		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	9	0
Upper-airway cough syndrome		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	3	0
Asthma		
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)
occurrences (all)	1	0
Dyspnoea exertional		
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)
occurrences (all)	1	0
Epistaxis		
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)
occurrences (all)	1	0
Increased viscosity of bronchial secretion		
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)
occurrences (all)	1	0
Lung hyperinflation		
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)
occurrences (all)	1	0
Nasal inflammation		
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)
occurrences (all)	1	0

Nasal oedema			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Painful respiration			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pleurisy			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Prolonged expiration			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Respiratory tract irritation			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Sinus polyp			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Sneezing			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Sputum discoloured			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Throat tightness			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 121 (4.96%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Insomnia			

subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Depression			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Abnormal dreams			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tobacco abuse			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Drug dependence			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Investigations			
Bacterial test positive			
subjects affected / exposed	7 / 121 (5.79%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Forced expiratory volume decreased			
subjects affected / exposed	6 / 121 (4.96%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Weight decreased			
subjects affected / exposed	5 / 121 (4.13%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
C-reactive protein increased			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Haemophilus test positive			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Liver function test abnormal			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	4	0	

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Atypical mycobacterium test positive subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Blood pressure increased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Body temperature increased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Pseudomonas test positive subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 4	0 / 4 (0.00%) 0	
Vitamin D decreased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Weight increased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Blood calcium decreased subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Blood glucose increased subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	

Blood urea increased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Crystal urine present			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Influenza A virus test positive			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Flavobacterium test positive			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Klebsiella test positive			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Streptococcus test positive			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ultrasound biliary tract abnormal			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Urinary sediment present			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Urine analysis abnormal			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vitamin A decreased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

White blood cells urine positive subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Pulmonary function test decreased subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Injury, poisoning and procedural complications			
Procedural pain subjects affected / exposed occurrences (all)	3 / 121 (2.48%) 3	0 / 4 (0.00%) 0	
Hand fracture subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	3 / 121 (2.48%) 3	0 / 4 (0.00%) 0	
Laceration subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Muscle strain subjects affected / exposed occurrences (all)	2 / 121 (1.65%) 2	0 / 4 (0.00%) 0	
Arthropod bite subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Arthropod sting subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Concussion subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Epicondylitis subjects affected / exposed occurrences (all)	1 / 121 (0.83%) 1	0 / 4 (0.00%) 0	
Fall			

subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Humerus fracture			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Joint dislocation			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ligament rupture			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Snake bite			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skeletal injury			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Soft tissue injury			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 121 (19.01%)	0 / 4 (0.00%)	
occurrences (all)	38	0	
Sinus headache			
subjects affected / exposed	9 / 121 (7.44%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Dizziness			
subjects affected / exposed	7 / 121 (5.79%)	0 / 4 (0.00%)	
occurrences (all)	8	0	

Migraine			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Hypoaesthesia			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Burning sensation			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hyperaesthesia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hypersomnia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Tinnitus			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Middle ear effusion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Otorrhoea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vertigo			

subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Blepharospasm			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis allergic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Eye swelling			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Photophobia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vitreous floaters			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	17 / 121 (14.05%)	0 / 4 (0.00%)	
occurrences (all)	24	0	
Diarrhoea			

subjects affected / exposed	17 / 121 (14.05%)	0 / 4 (0.00%)
occurrences (all)	25	0
Abdominal pain		
subjects affected / exposed	12 / 121 (9.92%)	0 / 4 (0.00%)
occurrences (all)	18	0
Vomiting		
subjects affected / exposed	12 / 121 (9.92%)	0 / 4 (0.00%)
occurrences (all)	13	0
Nausea		
subjects affected / exposed	9 / 121 (7.44%)	0 / 4 (0.00%)
occurrences (all)	10	0
Gastrooesophageal reflux disease		
subjects affected / exposed	7 / 121 (5.79%)	0 / 4 (0.00%)
occurrences (all)	7	0
Abdominal pain upper		
subjects affected / exposed	6 / 121 (4.96%)	0 / 4 (0.00%)
occurrences (all)	9	0
Abdominal distension		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	3	0
Tooth impacted		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	3	0
Abdominal discomfort		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Dental caries		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Flatulence		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Steatorrhoea		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Toothache		

subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Abdominal pain lower			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Barrett's oesophagus			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Defaecation urgency			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dental discomfort			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Palatal disorder			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pancreatitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Proctitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			

subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rectal polyp			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Food poisoning			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Bile duct stone			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 121 (4.96%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Eczema			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Rash erythematous			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Dermatitis contact			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis			

subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Eczema nummular			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Psoriasis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rash generalised			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Rosacea			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Subcutaneous nodule			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Acne			

subjects affected / exposed occurrences (all)	3 / 121 (2.48%) 3	0 / 4 (0.00%) 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 121 (7.44%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Back pain			
subjects affected / exposed	6 / 121 (4.96%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal pain			
subjects affected / exposed	5 / 121 (4.13%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Muscle spasms			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Osteopenia			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Pain in extremity			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Myalgia			
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Arthritis			

subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Bone pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Clubbing			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Metatarsalgia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Monarthrititis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	49 / 121 (40.50%)	0 / 4 (0.00%)	
occurrences (all)	85	0	
Nasopharyngitis			
subjects affected / exposed	21 / 121 (17.36%)	0 / 4 (0.00%)	
occurrences (all)	32	0	
Sinusitis			
subjects affected / exposed	18 / 121 (14.88%)	0 / 4 (0.00%)	
occurrences (all)	35	0	
Viral upper respiratory tract infection			
subjects affected / exposed	17 / 121 (14.05%)	0 / 4 (0.00%)	
occurrences (all)	23	0	
Upper respiratory tract infection			
subjects affected / exposed	15 / 121 (12.40%)	0 / 4 (0.00%)	
occurrences (all)	19	0	
Gastroenteritis viral			
subjects affected / exposed	9 / 121 (7.44%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
Oral candidiasis			
subjects affected / exposed	8 / 121 (6.61%)	0 / 4 (0.00%)	
occurrences (all)	13	0	
Influenza			
subjects affected / exposed	7 / 121 (5.79%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
Gastroenteritis			
subjects affected / exposed	5 / 121 (4.13%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Lower respiratory tract infection			
subjects affected / exposed	5 / 121 (4.13%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Acute sinusitis			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Vulvovaginal mycotic infection			

subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	6	0
Bacterial disease carrier		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	4	0
Lower respiratory tract infection bacterial		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	3	0
Pharyngitis streptococcal		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	4	0
Respiratory tract infection viral		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	4	0
Rhinitis		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	4	0
Tonsillitis		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	3	0
Upper respiratory tract infection bacterial		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	4	0
Urinary tract infection		
subjects affected / exposed	3 / 121 (2.48%)	0 / 4 (0.00%)
occurrences (all)	4	0
Bronchopulmonary aspergillosis allergic		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Laryngitis		
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)
occurrences (all)	2	0
Otitis externa		

subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Pharyngitis bacterial			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Viral infection			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Chronic sinusitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Croup infectious			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Diarrhoea infectious			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ear lobe infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Furuncle			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Haemophilus infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Infected dermal cyst			

subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Laryngitis viral			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Molluscum contagiosum			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Myringitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nasal abscess			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Oesophagitis bacterial			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Staphylococcal skin infection			

subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vaginitis bacterial			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Viral pharyngitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 121 (1.65%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Vitamin D deficiency			
subjects affected / exposed	4 / 121 (3.31%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Dehydration			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dyslipidaemia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

Fluid retention			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Impaired fasting glucose			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Increased appetite			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vitamin A deficiency			
subjects affected / exposed	1 / 121 (0.83%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2012	Clarified sample collection, statistical analysis plan and Early Termination visit details; updated follow-up timeframe; corrected pharmacogenomic analysis text.
05 December 2012	Extended study duration to 2 years; secondary objective was changed to evaluate the post-treatment safety of ivacaftor in subjects enrolled in the observational arm; pharmacokinetic (PK) blood sample collection was added to the ivacaftor arm; ophthalmologic examination was added to the safety endpoints and additional ophthalmologic examinations were added; contraceptive requirements were clarified; included a planned interim analysis for safety and efficacy data after all subjects completed Week 24 Visit.
01 April 2013	Subjects from Study 113 were offered enrollment in the ivacaftor arm of Study 112; clarified timing of Day 1 Visit in Study 112 with respect to Study 113; clarified that PK blood samples would not be collected from Study 113 subjects.
29 July 2013	Clarified that subjects from Study 113 must have completed the Study 113 Follow-up Visit and met responder criteria for eligibility to enroll in the Study 112 ivacaftor arm.
13 February 2014	Pregnancy language was revised; changed protocol to allow subjects to discontinue the study when Kalydeco was commercially-available and reimbursed for that indication in the subject's country; added optional exploratory hypertonic saline substudy; changed the timing of the planned interim analysis.
29 July 2014	Added an optional exploratory substudy for subjects with the G970R-CFTR Mutation.
08 December 2014	Made ophthalmologic examination assessments applicable to all subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported