

**Clinical trial results:****A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis who Have the R117H-CFTR Mutation****Summary**

EudraCT number	2012-000387-19
Trial protocol	GB
Global end of trial date	25 October 2013

**Results information**

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	07 August 2015

**Trial information****Trial identification**

Sponsor protocol code	VX11-770-110
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01614457
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, MA, 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)	EMEA-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	19 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 October 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of ivacaftor in subjects (6 years of age and older) with cystic fibrosis (CF) with R117H-CF transmembrane conductance regulator (CFTR) mutation.

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:

Subjects remained on their stable CF medication regimens from 4 weeks before Day 1 through the Follow up Visit.

Evidence for comparator: -

Actual start date of recruitment	03 July 2012
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?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	69
EEA total number of subjects	15

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)	17
Adolescents (12-17 years)	2
Adults (18-64 years)	48

From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 27 sites in the United States and the European Union.

### Pre-assignment

Screening details:

A total of 70 subjects were randomized, of which 1 subject discontinued the study prior to study drug administration. A total of 69 subjects started treatment.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ivacaftor

Arm description:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.

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

Dosage and administration details:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.

<b>Arm title</b>	Placebo
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Arm description:

Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.

<b>Number of subjects in period 1</b>	Ivacaftor	Placebo
Started	34	35
Completed	32	35
Not completed	2	0
'Non-Compliance '	1	-
'Pregnancy (Self or Partner) '	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Ivacaftor
Reporting group description: Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.	

Reporting group values	Ivacaftor	Placebo	Total
Number of subjects	34	35	69
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	29.2 ± 16.57	32.7 ± 17.43	-
Gender categorical Units: Subjects			
Female	19	20	39
Male	15	15	30

## End points

### End points reporting groups

Reporting group title	Ivacaftor
Reporting group description:	Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.
Reporting group title	Placebo
Reporting group description:	Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.

### Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24
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.  The analysis was performed on Full Analysis Set (FAS) which included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).
End point type	Primary
End point timeframe:	Baseline, Week 24

End point values	Ivacaftor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	35		
Units: Percent predicted of FEV1				
least squares mean (standard error)	2.5724 ( $\pm$ 1.1532)	0.4611 ( $\pm$ 1.1313)		

### Statistical analyses

Statistical analysis title	Ivacaftor vs Placebo
Statistical analysis description:	Analysis was based on mixed effects model for repeated measures (MMRM) with dependent variable absolute change from baseline, with treatment group, visit and treatment by visit interaction as fixed effects, subject as random effect, and with adjustment for the continuous baseline value of age and percent predicted FEV1, using compound symmetry covariance matrix.
Comparison groups	Ivacaftor v Placebo

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1979
Method	Mixed Model Repeated Measures
Parameter estimate	Least square (LS) Mean Difference
Point estimate	2.1114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1305
upper limit	5.3532

### Secondary: Change From Baseline in Body Mass Index (BMI) at Week 24

End point title	Change From Baseline in Body Mass Index (BMI) at Week 24
End point description: BMI was defined as weight in kilogram (kg) divided by height in square meter (m <sup>2</sup> ).	
FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Ivacaftor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	35		
Units: kg/m <sup>2</sup>				
least squares mean (standard error)	0.491 (± 0.6653)	0.2284 (± 0.6504)		

### Statistical analyses

Statistical analysis title	Ivacaftor vs Placebo
Statistical analysis description: Analysis was based on linear mixed model with dependent variable BMI and treatment as a fixed effect, adjustment for baseline percent predicted FEV1, age and visit by treatment interaction was included as covariates and intercept, visit were included as random effects.	
Comparison groups	Ivacaftor v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.778 <sup>[1]</sup>
Method	Linear Mixed Model
Parameter estimate	LS Mean difference
Point estimate	0.2626

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5698
upper limit	2.095

Notes:

[1] - p-value for the treatment effect is from the slope of BMI versus time.

### Secondary: Change From Baseline in Sweat Chloride Through Week 24

End point title	Change From Baseline in Sweat Chloride Through Week 24
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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.

FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Ivacaftor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	35		
Units: millimole per liter (mmol/L				
least squares mean (standard error)	-26.2771 ( $\pm$ 1.4584)	-2.3078 ( $\pm$ 1.3716)		

### Statistical analyses

Statistical analysis title	Ivacaftor vs Placebo
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Statistical analysis description:

Analysis was based on MMRM with dependent variable absolute change from baseline, with treatment group, visit and treatment by visit interaction as fixed effects, subject as random effect, and with adjustment for the continuous baseline value of age and percent predicted FEV1, and sweat chloride, using a compound symmetry covariance matrix.

Comparison groups	Ivacaftor v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-23.9693
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.0094
upper limit	-19.9293

## Secondary: Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 24

End point title	Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 24
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End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. 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.

FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). Here, "Number of participants analyzed" signifies those subjects who were evaluable for this measure.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Ivacaftor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: units on a scale				
least squares mean (standard error)	7.5585 ( $\pm$ 2.2073)	-0.8289 ( $\pm$ 2.1569)		

## Statistical analyses

Statistical analysis title	Ivacaftor vs Placebo
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Statistical analysis description:

Analysis was based on MMRM with dependent variable absolute change from baseline, with treatment group, visit and treatment by visit interaction as fixed effects, subject as random effect, and with adjustment for the continuous baseline value of age and percent predicted FEV1, and CFQ-R respiratory domain score, using compound symmetry covariance matrix.

Comparison groups	Ivacaftor v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0091
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	8.3874
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1658
upper limit	14.609

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**Secondary: Time to First Pulmonary Exacerbation**

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End point title	Time to First Pulmonary Exacerbation
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End point description:

Number of events (pulmonary exacerbation) during the pre-specified time intervals were reported. A subject without an exacerbation before withdrawal from the study was considered censored at the time of withdrawal, and a subject without an exacerbation who completes the study period was considered censored at the end of the analysis period.

FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).

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End point type	Secondary
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End point timeframe:

Day 0 to 15, Day 16 to 56, Day 57 to 112, Day 113 to 168

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<b>End point values</b>	Ivacaftor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	35		
Units: Events				
Day 0 to 15	3	1		
Day 16 to 56	4	2		
Day 57 to 112	2	6		
Day 113 to 168	1	4		

**Statistical analyses**

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<b>Statistical analysis title</b>	Ivacaftor vs Placebo
Comparison groups	Ivacaftor v Placebo
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8556
Method	Cox Proportional Hazard Regression

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**Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)**

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End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)
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End point description:

AE: any untoward medical occurrence, including clinically significant clinical laboratory assessments which occurs during course of study, whether it is considered related to study drug or not. SAE: medical event or condition, which falls into any of following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolonged hospitalization,

persistent/significant disability/incapacity, congenital anomaly/birth defect, important medical event. Safety Set included all subjects who received at least 1 dose of study drug (ivacaftor or placebo).

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End point type	Secondary
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End point timeframe:

Baseline up to follow-up (3 to 4 weeks after last dose [last dose = Week 24])

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<b>End point values</b>	Ivacaftor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	35		
Units: Subjects				
Subjects with any AEs	32	35		
Subjects with SAEs	4	6		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow-up (3 to 4 weeks after last dose [last dose = Week 24])

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
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Reporting group description:

Ivacaftor 150 mg tablet orally twice daily for 24 weeks.

Reporting group title	Placebo
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Reporting group description:

Placebo-matched-to-ivacaftor tablet orally twice daily for 24 weeks.

<b>Serious adverse events</b>	Ivacaftor	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 34 (11.76%)	6 / 35 (17.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (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	3 / 34 (8.82%)	6 / 35 (17.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Ivacaftor	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 34 (94.12%)	35 / 35 (100.00%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 34 (5.88%)	6 / 35 (17.14%)	
occurrences (all)	3	9	
Fatigue			
subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Influenza like illness			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Chills			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Immune system disorders			

Hypersensitivity subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 35 (5.71%) 2	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	10 / 34 (29.41%) 14	9 / 35 (25.71%) 12	
Sputum increased subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 6	4 / 35 (11.43%) 4	
Nasal congestion subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 7	2 / 35 (5.71%) 3	
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 5	2 / 35 (5.71%) 4	
Haemoptysis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	6 / 35 (17.14%) 10	
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 4	3 / 35 (8.57%) 3	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	2 / 35 (5.71%) 2	
Wheezing subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 4	1 / 35 (2.86%) 1	
Nasal oedema subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	2 / 35 (5.71%) 2	
Rales subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	3 / 35 (8.57%) 4	
Upper-airway cough syndrome			

subjects affected / exposed	3 / 34 (8.82%)	0 / 35 (0.00%)
occurrences (all)	3	0
Nasal mucosal disorder		
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Paranasal sinus hypersecretion		
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)
occurrences (all)	1	1
Sinus congestion		
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Asthma		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	2
Bronchospasm		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Nasal turbinate abnormality		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Pleural effusion		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Pleurisy		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Pleuritic pain		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Respiration abnormal		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Respiratory tract congestion		
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	1	0
Tonsillolith		

subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 35 (0.00%) 0	
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 35 (5.71%) 2	
Anxiety			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Insomnia			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 4	2 / 35 (5.71%) 3	
Blood potassium increased			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 35 (5.71%) 2	
C-reactive protein increased			
subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 2	1 / 35 (2.86%) 1	
Alanine aminotransferase increased			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Blood bilirubin increased			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Blood calcium decreased			
subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Blood creatine phosphokinase increased			
subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 35 (0.00%) 0	
Blood pressure increased			

subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Platelet count increased			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Pulmonary function test decreased			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
White blood cells urine positive			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Anal injury			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Animal bite			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hand fracture			

subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Periorbital haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Tendon rupture			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 34 (17.65%)	5 / 35 (14.29%)	
occurrences (all)	9	6	
Dizziness			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Lethargy			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Sinus headache			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear congestion			

subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	2	
Ear pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
<b>Gastrointestinal disorders</b>			
Diarrhoea			
subjects affected / exposed	5 / 34 (14.71%)	4 / 35 (11.43%)	
occurrences (all)	6	4	
Vomiting			
subjects affected / exposed	3 / 34 (8.82%)	4 / 35 (11.43%)	
occurrences (all)	3	4	
Abdominal pain			
subjects affected / exposed	4 / 34 (11.76%)	0 / 35 (0.00%)	
occurrences (all)	5	0	
Abdominal pain upper			
subjects affected / exposed	2 / 34 (5.88%)	2 / 35 (5.71%)	
occurrences (all)	5	3	
Constipation			
subjects affected / exposed	0 / 34 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Abdominal discomfort			
subjects affected / exposed	2 / 34 (5.88%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Abdominal tenderness			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Loose tooth			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	

Palatal oedema subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 35 (0.00%) 0	
<b>Skin and subcutaneous tissue disorders</b>			
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Drug eruption subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Eczema subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Ingrowing nail subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
Rosacea subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	0 / 35 (0.00%) 0	
<b>Renal and urinary disorders</b>			
Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	1 / 35 (2.86%) 1	
<b>Musculoskeletal and connective tissue disorders</b>			
Arthralgia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	4 / 35 (11.43%) 4	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	2 / 35 (5.71%) 2	
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	1 / 35 (2.86%) 1	

Myalgia			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Clubbing			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Exostosis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	11 / 34 (32.35%)	13 / 35 (37.14%)	
occurrences (all)	14	18	
Upper respiratory tract infection			
subjects affected / exposed	3 / 34 (8.82%)	5 / 35 (14.29%)	
occurrences (all)	3	6	
Sinusitis			
subjects affected / exposed	2 / 34 (5.88%)	5 / 35 (14.29%)	
occurrences (all)	4	6	
Bacterial disease carrier			
subjects affected / exposed	3 / 34 (8.82%)	1 / 35 (2.86%)	
occurrences (all)	6	1	
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Acute sinusitis			
subjects affected / exposed	1 / 34 (2.94%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Bronchitis		
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	1	0
Candidiasis		
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	1	0
Ear infection		
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	2	0
Folliculitis		
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Lip infection		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Nasopharyngitis		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Oral fungal infection		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Oral herpes		
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)
occurrences (all)	1	0
Otitis externa		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)
occurrences (all)	0	1
Scarlet fever		

subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Varicella			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 34 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Decreased appetite			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	1 / 34 (2.94%)	0 / 35 (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	An additional screening assessment of a comprehensive ophthalmologic examination was added for all subjects. Following feedback from Cystic Fibrosis Foundation Therapeutics, the number of electrocardiogram (ECG) assessments was reduced to shorten the duration of a study visit. -An inflammatory mediator assessment was added to the Follow-up Visit.
15 June 2012	Abstinence was removed as a highly effective method of contraception for a subject's partner since this method would only be effective when practiced with a study subject who was also practicing abstinence.
18 December 2012	Collection of sweat chloride at Screening was required for subjects only if the value is not available in the subject's medical records and the value was needed for the diagnosis of CF to fulfill inclusion criterion. Changed the timing of when the Follow-up Visit was to occur after the last dose of study drug from "4 weeks ( $\pm$ 7 days)" to "3 to 4 weeks" in protocol -Ophthalmologic examinations were added as a safety endpoint for safety monitoring. Commercially available ivacaftor (Kalydeco™) was added to the list of prohibited medications. Clarified the statistical analysis was to be performed for the interim analysis. Requirement in protocol was changed to completing a case report form (CRF) for each subject screened in order to collect data for subjects who were screened but not enrolled.
11 June 2013	The exclusion of hypertonic saline use was removed. A recommendation was added that subjects should maintain their status of hypertonic saline use for the duration of the study and the final analysis was to be based on data from all enrolled subject assessments. Clarification was provided that, in the event of early study termination, subjects who had not had their Week 24 Visit were to be considered to have completed their assigned treatment duration.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrollment was planned for a min of 40 & a max of approx. 80 subjects. Based upon power calculations & after exceeding min number of subjects defined in protocol, study was stopped by sponsor; however, the overall study status was completed.

Notes: