Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of VX 770 in Subjects with Cystic Fibrosis and the G551D Mutation

Summary

EudraCT number	2008-007416-15
Trial protocol	IE GB DE CZ FR
Global end of trial date	29 November 2012

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	VX08-770-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00909532
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, +1 617-444-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex, +1 617-444-6777, 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	15 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 November 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of VX-770 after 24 weeks of treatment in subjects with cystic fibrosis (CF) with G551D cystic fibrosis 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: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2009
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: 9
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Ireland: 14
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United States: 91
Worldwide total number of subjects	161
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	36
Adults (18-64 years)	125
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started on 10 June 2009 (signing of first informed consent). After obtaining consent and assent (where applicable), screening evaluations were completed during a period of 2 to 5 weeks (Day -35 to Day -15) before the first dose of study drug.

Pre-assignment

Screening details:

A total of 167 subjects were randomized; 161 subjects received at least 1 dose of the study drug. A 2-week run-in period was included to establish the baseline assessments on Day 1 after ensuring that subjects were properly taking their cystic fibrosis (CF) medication regimens.

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
Arm title	Placebo

Arm description:

Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks.

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

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally q12h up to 48 weeks.

Arm title	150 mg Ivacaftor q12h

Arm description:

Ivacaftor 150 mg tablet orally q12h for up to 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor 150 mg tablet administered orally q12h for up to 48 weeks.

Number of subjects in period 1	Placebo	150 mg Ivacaftor q12h
Started	78	83
Completed Treatment Period, Week 24	71	80
Completed	68	77
Not completed	10	6
Physician decision	1	-
Consent withdrawn by subject	1	1
'Wrong Genotype '	1	-
Pregnancy	-	1
Adverse event	4	1
'Increased Lab Draws, Difficult Lab Stick '	1	-
Noncompliance with Study Requirements	-	2
Prohibited Medication	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks.	
Reporting group title	150 mg Ivacaftor q12h
Reporting group description:	
Ivacaftor 150 mg tablet orally q12h for up to 48 weeks.	

Reporting group values	Placebo	150 mg Ivacaftor q12h	Total
Number of subjects	78	83	161
Age categorical Units: Subjects			
<=18 years	17	19	36
Between 18 and 65 years	61	64	125
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	24.7	26.2	
standard deviation	± 9.21	± 9.85	-
Gender categorical Units: Subjects			
Female	40	44	84
Male	38	39	77
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	77	81	158
Unknown or Not Reported	1	2	3
Race/Ethnicity, Customized Units: Subjects			
White	77	81	158
Not Allowed to Ask Per Local Regulations	1	2	3
Region of Enrollment Units: Subjects			
North America	50	50	100
Europe	19	23	42
Australia	9	10	19
Percent Predicted FEV1, Categorical Units: Subjects			
< 70% predicted FEV1	45	49	94
≥ 70% predicted FEV1	33	34	67
Percent Predicted Forced Expiratory Volume in 1 Second (FEV1), Continuous [1] Units: percentage			
arithmetic mean	63.7	63.5	

standard deviation	± 16.83	± 16.14	-
Weight			
Units: kilograms			
arithmetic mean	61.2	61.7	
standard deviation	± 13.93	± 14.26	-
Body Mass Index			
Units: kilograms per square meter			
arithmetic mean	21.9	21.7	
standard deviation	± 3.49	± 3.65	-
Sweat Chloride			
Units: millimoles per liter (mmol/liter)			
arithmetic mean	100.1	100.4	
standard deviation	± 10.63	± 10	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks.	
Reporting group title	150 mg Ivacaftor q12h
Reporting group description:	
Ivacaftor 150 mg tablet orally q12h for up to 48 weeks.	

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

End point title	Absolute Mean Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24
End point description:	
Spirometry (as measured by FEV1) is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies. Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.	
End point type	Primary
End point timeframe:	
Baseline through 24 weeks	

End point values	Placebo	150 mg Ivacaftor q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: percent of predicted volume (L)				
least squares mean (standard error)	-0.2 (± 0.7)	10.4 (± 0.7)		

Statistical analyses

Statistical analysis title	Percent Predicted FEV1 Through Week 24
Statistical analysis description:	
The primary analysis for the primary efficacy variable was based on a Mixed-Effects Model for Repeated Measures (MMRM). The model included absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) as the dependent variable, treatment (ivacaftor versus placebo) and visit (Day 15, Week 8, Week 16, and Week 24) as fixed effects, and subject as a random effect, with adjustment for the continuous baseline values of age and percent predicted FEV1.	
Comparison groups	Placebo v 150 mg Ivacaftor q12h

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	10.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.6
upper limit	12.6
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[1] - The primary and key secondary endpoints were analyzed using Hochberg's step-up procedure: test 1, primary (α=0.05); test 2, CFQ-R resp domain (Wk24) and sweat chloride (Wk24)(α=0.05).

Secondary: Absolute Mean Change From Baseline in Percent Predicted FEV1 Through Week 48

End point title	Absolute Mean Change From Baseline in Percent Predicted FEV1 Through Week 48

End point description:

Spirometry (as measured by FEV1) is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies.

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

End point type	Secondary

End point timeframe:

Baseline through 48 weeks

End point values	Placebo	150 mg Ivacaftor q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: percent of predicted volume (L)				
least squares mean (standard error)	-0.4 (± 0.7)	10.1 (± 0.7)		

Statistical analyses

Statistical analysis title	Percent Predicted FEV1 Through Week 48

Statistical analysis description:

Analysis of this variable was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were obtained from Mixed-Effects Model for Repeated Measures (MMRM) with dependent variable absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for the continuous baseline values of age and percent predicted forced expiratory volume in 1 second (FEV1),using unstructured covariance matrix.

Comparison groups	Placebo v 150 mg Ivacaftor q12h

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.5
upper limit	12.5
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[2] - There was no adjustment for multiple comparisons. Denominator degrees of freedom were estimated using the Kenward-Roger approximation. No imputation of missing data was done.

Secondary: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score Through Week 24 and Week 48 (Respiratory Domain Score, Pooled)

End point title	Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score Through Week 24 and Week 48 (Respiratory Domain Score, Pooled)

End point description:

The CFQ-R is a health-related quality of life measure for subjects with cystic fibrosis. Each domain is scored from 0 (worst) to 100 (best). A difference of at least 4 points in the respiratory domain score of the CFQ-R is considered a minimal clinically important difference (MCID).

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

End point type	Secondary

End point timeframe:

Baseline through 24 weeks and 48 weeks

End point values	Placebo	150 mg Ivacaftor q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	80		
Units: score on a scale				
least squares mean (standard error)				
Change from Baseline Through Week 24	-2.1 (± 1.3)	6 (± 1.2)		
Change from Baseline Through Week 48	-2.7 (± 1.2)	6 (± 1.1)		

Statistical analyses

Statistical analysis title	CFQ-R Score Through Week 24

Statistical analysis description:

Through Week 24: Analysis for the respiratory domain score endpoint was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from Mixed-Effects Model for Repeated Measures (MMRM) with dependent variable absolute change from baseline, fixed effects for categorical

visit and treatment group, and adjustment for continuous baseline value for age, domain score, and percent predicted FEV1, using unstructured covariance matrix.

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	11.4
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[3] - Analyzed in sequence: test 1, primary (α=0.05); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) (α=0.05).

Statistical analysis title	CFQ-R Score Through Week 48

Statistical analysis description:

Through Week 48: Analysis for the CFQ-R respiratory domain score endpoint was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from MMRM with dependent variable absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for continuous baseline value for age,sweat chloride, and percent predicted FEV1,using unstructured covariance matrix

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	11.9
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[4] - There was no adjustment for multiple comparisons.

Secondary: Absolute Change From Baseline in Sweat Chloride Concentration Through Week 24 and Week 48

End point title	Absolute Change From Baseline in Sweat Chloride Concentration Through Week 24 and Week 48

End point description:

The sweat chloride (quantitative pilocarpine iontophoresis) test is a standard diagnostic tool for cystic fibrosis (CF), serving as an indicator of cystic fibrosis transmembrane conductance regulator (CFTR) activity.

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

End point type	Secondary

End point timeframe:

Baseline through 24 weeks and 48 weeks

End point values	Placebo	150 mg Ivacaftor q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	78		
Units: millimoles per liter				
least squares mean (standard error)				
Change from Baseline Through Week 24	-0.8 (± 1.3)	-48.7 (± 1.2)		
Change from Baseline Through Week 48	-0.6 (± 1.3)	-48.7 (± 1.2)		

Statistical analyses

Statistical analysis title	Sweat Chloride Concentration Through Week 24

Statistical analysis description:

Through Week 24: Analysis for this variable was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from Mixed-Effects Model for Repeated Measures (MMRM) with dependent variable absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for continuous baseline value for age, sweat chloride, and percent predicted FEV1, using unstructured covariance matrix.

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-47.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.3
upper limit	-44.5
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[5] - Analyzed in sequence: test 1, primary (α=0.05); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) (α=0.05); test 3 using Hochberg's on time to pulmonary exacerbation (Wk 48) and weight (Wk 48).

Statistical analysis title	Sweat Chloride Concentration Through Week 48

Statistical analysis description:

Through Week 48: Analysis for this variable was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from Mixed-Effects Model for Repeated Measures (MMRM) with dependent variable absolute change from baseline, fixed effects for categorical visit and treatment

group, and adjustment for continuous baseline value for age, sweat chloride, and percent predicted FEV1, using unstructured covariance matrix.

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-48.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.5
upper limit	-44.7
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[6] - There was no adjustment for multiple comparisons.

Secondary: Time-to-first Pulmonary Exacerbation Through Week 24 and Week 48

End point title	Time-to-first Pulmonary Exacerbation Through Week 24 and Week 48

End point description:

Pulmonary exacerbation was defined as a change in antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of signs/symptoms such as change in sputum; new or increased hemoptysis; increased cough or dyspnea; malaise, fatigue, or lethargy; temperature above 38 degrees C; anorexia or weight loss; sinus pain/tenderness and discharge; change in physical examination of the chest; decreased pulmonary function by 10%; and radiographic changes indicative of pulmonary infection.

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

End point type	Secondary

End point timeframe:

Baseline through 24 weeks and 48 weeks

End point values	Placebo	150 mg Ivacaftor q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: proportion of event-free participants				
number (confidence interval 95%)				
0 to 15 Days	0.97 (0.9 to 0.99)	0.98 (0.91 to 0.99)		
16 to 56 Days	0.87 (0.77 to 0.93)	0.89 (0.8 to 0.94)		
57 to 112 Days	0.72 (0.61 to 0.81)	0.83 (0.73 to 0.9)		
113 to 168 Days	0.53 (0.41 to 0.64)	0.78 (0.68 to 0.86)		
169 to 224 Days	0.51 (0.39 to 0.61)	0.75 (0.64 to 0.83)		

225 to 280 Days	0.44 (0.32 to 0.55)	0.7 (0.58 to 0.78)		
281 to 336 Days	0.41 (0.29 to 0.52)	0.67 (0.55 to 0.76)		

Statistical analyses

Statistical analysis title	first Pulmonary Exacerbation Through Week 24

Statistical analysis description:

Time to first pulmonary exacerbation through Week 24 was analyzed using Cox regression. The model included a covariate for treatment and adjustments for the age group and percent predicted forced expiratory volume in 1 second (FEV1) severity at baseline.

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [7]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.71

Notes:

[7] - Analyzed in sequence: test 1, primary (α=0.05); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) (α=0.05); test 3 using Hochberg's on time to pulmonary exacerbation (Wk 48) and weight (Wk 48).

Statistical analysis title	first Pulmonary Exacerbation Through Week 48

Statistical analysis description:

Time to first pulmonary exacerbation through Week 48 was analyzed using Cox regression. The model included a covariate for treatment and adjustments for the age group and percent predicted forced expiratory volume in 1 second (FEV1) severity at baseline

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [8]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.73

Notes:

[8] - Analyzed in sequence: test 1, primary (α=0.05); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) (α=0.05); test 3 using Hochberg's on time to pulmonary exacerbation (Wk 48) and weight (Wk 48).

Secondary: Absolute Change From Baseline in Weight at Week 24 and Week 48

End point title	Absolute Change From Baseline in Weight at Week 24 and Week 48

End point description:

As malnutrition is common in subjects with cystic fibrosis (CF) because of increased energy expenditures due to lung disease and fat malabsorption, body weight is an important clinical measure of nutritional status.

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

End point type	Secondary

End point timeframe:

Baseline to 24 weeks and 48 weeks

End point values	Placebo	150 mg Ivacaftor q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: kilograms				
least squares mean (standard error)				
At Week 24	0.2 (± 0.4)	3 (± 0.4)		
At Week 48	0.4 (± 0.5)	3.1 (± 0.5)		

Statistical analyses

Statistical analysis title	Weight at Week 24

Statistical analysis description:

At Week 24: Analysis for this variable was based on a linear mixed effects (LME) model with treatment as a fixed effect, and intercept, visit (days on study) and treatment by visit interaction as random effects, with adjustment for age group and baseline percent predicted forced expiratory volume in 1 second (FEV1) severity

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	0.5

Statistical analysis title	Weight at Week 48

Statistical analysis description:

At Week 48: Analysis for this variable was based on a linear mixed effects (LME) model with treatment as a fixed effect and visit (days on study) and treatment by visit interaction as random effects, with adjustment for age group and baseline percent predicted forced expiratory volume in 1 second (FEV1) severity.

Comparison groups	Placebo v 150 mg Ivacaftor q12h
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	4.1
Variability estimate	Standard error of the mean
Dispersion value	0.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For enrolled subjects, adverse events were collected through the Follow-up Visit (4 weeks [± 7 days] after the last dose of study drug).

Adverse event reporting additional description:

For subjects who were screened but were not subsequently enrolled in the study, non-serious adverse event (AEs) were not collected, but serious adverse events (SAEs) were reported. For subjects who completed 48 weeks of study drug treatment and enrolled in the open-label extension study, adverse events were only collected through the Week 48 Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks.

Reporting group title	150 mg Ivacaftor q12h

Reporting group description:

Ivacaftor 150 mg tablet orally every 12 hours (q12h) up to 48 weeks.

Serious adverse events	Placebo	150 mg Ivacaftor q12h	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 78 (42.31%)	20 / 83 (24.10%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter Related Complication			

subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (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	4 / 78 (5.13%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (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 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	26 / 78 (33.33%)	11 / 83 (13.25%)	
occurrences causally related to treatment / all	4 / 37	3 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting1			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (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			
Haematuria			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (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			
Implant site infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myringitis bullous			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	150 mg Ivacaftor q12h	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 78 (100.00%)	82 / 83 (98.80%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Peripheral Coldness			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Poor peripheral circulation			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 78 (11.54%)	10 / 83 (12.05%)	
occurrences (all)	11	13	

Fatigue			
subjects affected / exposed	7 / 78 (8.97%)	7 / 83 (8.43%)	
occurrences (all)	9	8	
Non-cardiac chest pain			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	4	3	
Chest discomfort			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Chills			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Malaise			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Application site burn			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Application site dermatitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Application site scar			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Axillary pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Catheter Related Complication			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	

Catheter Thrombosis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Exercise tolerance decreased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Food allergy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Balanitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Breast inflammation			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Breast Mass			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Epididymitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Gynaecomastia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Nipple disorder			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Nipple pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Oligomenorrhoea			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Ovarian cyst			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Prostatitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	33 / 78 (42.31%)	27 / 83 (32.53%)	
occurrences (all)	59	38	
Oropharyngeal pain			
subjects affected / exposed	15 / 78 (19.23%)	17 / 83 (20.48%)	
occurrences (all)	23	25	
Nasal congestion			
subjects affected / exposed	12 / 78 (15.38%)	17 / 83 (20.48%)	
occurrences (all)	17	22	
Haemoptysis			

subjects affected / exposed	15 / 78 (19.23%)	9 / 83 (10.84%)	
occurrences (all)	21	17	
Productive cough			
subjects affected / exposed	11 / 78 (14.10%)	12 / 83 (14.46%)	
occurrences (all)	19	15	
Rales			
subjects affected / exposed	8 / 78 (10.26%)	9 / 83 (10.84%)	
occurrences (all)	14	17	
Respiratory tract congestion			
subjects affected / exposed	6 / 78 (7.69%)	6 / 83 (7.23%)	
occurrences (all)	9	7	
Sinus congestion			
subjects affected / exposed	4 / 78 (5.13%)	8 / 83 (9.64%)	
occurrences (all)	4	9	
Rhinorrhoea			
subjects affected / exposed	6 / 78 (7.69%)	4 / 83 (4.82%)	
occurrences (all)	6	4	
Paranasal sinus hypersecretion			
subjects affected / exposed	6 / 78 (7.69%)	3 / 83 (3.61%)	
occurrences (all)	7	3	
Wheezing			
subjects affected / exposed	3 / 78 (3.85%)	5 / 83 (6.02%)	
occurrences (all)	3	8	
Dyspnoea			
subjects affected / exposed	5 / 78 (6.41%)	2 / 83 (2.41%)	
occurrences (all)	5	2	
Pleuritic pain			
subjects affected / exposed	2 / 78 (2.56%)	5 / 83 (6.02%)	
occurrences (all)	2	7	
Dysphonia			
subjects affected / exposed	3 / 78 (3.85%)	3 / 83 (3.61%)	
occurrences (all)	3	3	
Respiration abnormal			
subjects affected / exposed	4 / 78 (5.13%)	2 / 83 (2.41%)	
occurrences (all)	5	2	
Epistaxis			

subjects affected / exposed	1 / 78 (1.28%)	3 / 83 (3.61%)	
occurrences (all)	1	4	
Lung hyperinflation			
subjects affected / exposed	2 / 78 (2.56%)	2 / 83 (2.41%)	
occurrences (all)	3	3	
Nasal mucosal disorder			
subjects affected / exposed	2 / 78 (2.56%)	2 / 83 (2.41%)	
occurrences (all)	2	2	
Increased viscosity of bronchial secretion			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Nasal inflammation			
subjects affected / exposed	0 / 78 (0.00%)	3 / 83 (3.61%)	
occurrences (all)	0	3	
Nasal turbinate abnormality			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	2	2	
Pharyngeal erythema			
subjects affected / exposed	0 / 78 (0.00%)	3 / 83 (3.61%)	
occurrences (all)	0	3	
Rhinitis allergic			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Rhonchi			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	4	
Asthma			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Postnasal Drip			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Pulmonary congestion			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	

Sinus disorder			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Sputum discoloured			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	3	0	
Sputum retention			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Throat irritation			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Bronchial secretion retention			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Hypoventilation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Nasal oedema			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Nasal polyps			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Painful respiration			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Prolonged expiration			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	

Sneezing			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Stridor			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 78 (1.28%)	3 / 83 (3.61%)	
occurrences (all)	1	3	
Abnormal dreams			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Libido decreased			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Sleep disorder			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Affect lability			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Affective disorder			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Panic attack			

subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Tobacco withdrawal symptoms			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	11 / 78 (14.10%)	3 / 83 (3.61%)	
occurrences (all)	14	3	
Alanine aminotransferase increased			
subjects affected / exposed	5 / 78 (6.41%)	5 / 83 (6.02%)	
occurrences (all)	6	9	
C-reactive protein increased			
subjects affected / exposed	5 / 78 (6.41%)	4 / 83 (4.82%)	
occurrences (all)	6	4	
Blood glucose increased			
subjects affected / exposed	3 / 78 (3.85%)	5 / 83 (6.02%)	
occurrences (all)	3	6	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 78 (2.56%)	5 / 83 (6.02%)	
occurrences (all)	2	7	
Bacteria Sputum Identified			
subjects affected / exposed	1 / 78 (1.28%)	6 / 83 (7.23%)	
occurrences (all)	1	7	
Hepatic enzyme increased			
subjects affected / exposed	3 / 78 (3.85%)	4 / 83 (4.82%)	
occurrences (all)	4	4	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 78 (3.85%)	3 / 83 (3.61%)	
occurrences (all)	4	6	
Breath sounds abnormal			
subjects affected / exposed	4 / 78 (5.13%)	2 / 83 (2.41%)	
occurrences (all)	5	2	
Weight decreased			

subjects affected / exposed	4 / 78 (5.13%)	2 / 83 (2.41%)	
occurrences (all)	4	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	4	5	
Sputum abnormal			
subjects affected / exposed	2 / 78 (2.56%)	3 / 83 (3.61%)	
occurrences (all)	2	3	
Urine leukocyte esterase positive			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Blood glucose decreased			
subjects affected / exposed	3 / 78 (3.85%)	1 / 83 (1.20%)	
occurrences (all)	4	1	
Blood urine present			
subjects affected / exposed	2 / 78 (2.56%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Prothrombin time prolonged			
subjects affected / exposed	1 / 78 (1.28%)	3 / 83 (3.61%)	
occurrences (all)	1	3	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	3	
Blood bilirubin increased			
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)	
occurrences (all)	2	3	
Forced expiratory volume decreased			
subjects affected / exposed	3 / 78 (3.85%)	0 / 83 (0.00%)	
occurrences (all)	4	0	
International normalised ratio increased			
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)	
occurrences (all)	2	1	
Vitamin D decreased			

subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
White blood cell count increased			
subjects affected / exposed	3 / 78 (3.85%)	0 / 83 (0.00%)	
occurrences (all)	4	0	
Blood glucose fluctuation			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Blood immunoglobulin E increased			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Glucose urine present			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Neutrophil count increased			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	6	0	
Bacterial Antibody Positive			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Blood immunoglobulin G increased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Full blood count abnormal			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Fungus Sputum Test Positive			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	

Gastrointestinal examination abnormal				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Haemoglobin decreased				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Liver function test abnormal				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Liver palpable subcostal				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Lymphocyte count decreased				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Monocyte count increased				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	2	0		
Platelet count decreased				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Protein urine present				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Specific gravity urine increased				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Spirometry abnormal				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Transaminases increased				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Weight increased				

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
ELECTROCARDIOGRAM ST-T CHANGE			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Joint Sprain			
subjects affected / exposed	4 / 78 (5.13%)	0 / 83 (0.00%)	
occurrences (all)	5	0	
Contusion			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Limb injury			
subjects affected / exposed	0 / 78 (0.00%)	3 / 83 (3.61%)	
occurrences (all)	0	3	
Procedural pain			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Excoriation			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Hand fracture			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Arthropod bite			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Burns second degree			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Concussion			

subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Foot fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Joint dislocation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Medication error			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Skeletal injury			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Stress fracture			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Sunburn			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	39 / 78 (50.00%)	29 / 83 (34.94%)	
occurrences (all)	77	47	
Cystic fibrosis related diabetes			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 78 (0.00%)	3 / 83 (3.61%)	
occurrences (all)	0	3	
Tachycardia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Extrasystoles			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Left ventricular dysfunction			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 78 (16.67%)	19 / 83 (22.89%)	
occurrences (all)	31	39	
Dizziness			
subjects affected / exposed	1 / 78 (1.28%)	10 / 83 (12.05%)	
occurrences (all)	1	11	
Sinus headache			
subjects affected / exposed	4 / 78 (5.13%)	6 / 83 (7.23%)	
occurrences (all)	4	6	
Migraine			
subjects affected / exposed	2 / 78 (2.56%)	3 / 83 (3.61%)	
occurrences (all)	3	3	
Lethargy			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Aphonia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Cognitive disorder			

subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Hemicephalalgia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Hyposmia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 78 (2.56%)	3 / 83 (3.61%)	
occurrences (all)	2	3	
Anaemia			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Eosinophilia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	

Iron deficiency anaemia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Lymph node pain			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Lymphadenitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 78 (0.00%)	4 / 83 (4.82%)	
occurrences (all)	0	4	
Ear pain			
subjects affected / exposed	1 / 78 (1.28%)	3 / 83 (3.61%)	
occurrences (all)	1	3	
Deafness			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Tinnitus			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Ear congestion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Ear pruritus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Middle ear effusion			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Vestibular disorder			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	2	2	
Dry eye			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 78 (12.82%)	13 / 83 (15.66%)	
occurrences (all)	13	14	
Nausea			
subjects affected / exposed	9 / 78 (11.54%)	13 / 83 (15.66%)	
occurrences (all)	12	22	
Diarrhoea			
subjects affected / exposed	10 / 78 (12.82%)	11 / 83 (13.25%)	
occurrences (all)	12	12	
Vomiting			
subjects affected / exposed	10 / 78 (12.82%)	9 / 83 (10.84%)	
occurrences (all)	10	13	
Abdominal pain upper			
subjects affected / exposed	6 / 78 (7.69%)	4 / 83 (4.82%)	
occurrences (all)	7	5	
Constipation			
subjects affected / exposed	5 / 78 (6.41%)	1 / 83 (1.20%)	
occurrences (all)	5	1	
Flatulence			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	5	2	
Abdominal discomfort			

subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)		
occurrences (all)	2	1		
Gastrooesophageal reflux disease				
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)		
occurrences (all)	2	1		
Toothache				
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)		
occurrences (all)	1	2		
Abdominal distension				
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)		
occurrences (all)	6	1		
Abdominal pain lower				
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)		
occurrences (all)	1	1		
Faeces pale				
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)		
occurrences (all)	0	2		
Gastritis				
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)		
occurrences (all)	0	2		
Haemorrhoids				
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)		
occurrences (all)	2	0		
Abdominal tenderness				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Distal intestinal obstruction syndrome				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
DRY MOUTH				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Dyspepsia				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		

Frequent bowel movements			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Pancreatitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Post-tussive vomiting			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Steatorrhoea			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Tooth impacted			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Cytolytic Hepatitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 78 (5.13%)	12 / 83 (14.46%)	
occurrences (all)	4	22	
Acne			
subjects affected / exposed	3 / 78 (3.85%)	6 / 83 (7.23%)	
occurrences (all)	3	6	
Pruritus			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Dry skin			

subjects affected / exposed	3 / 78 (3.85%)	1 / 83 (1.20%)	
occurrences (all)	3	1	
Erythema			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Night sweats			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Rash erythematous			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Rash macular			
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)	
occurrences (all)	2	1	
Alopecia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Eczema			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	4	0	
Rash maculo-papular			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Dermatitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Dermatitis acneiform			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Drug eruption			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Hair texture abnormal			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Heat Rash			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia Facial			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Photosensitivity Allergic Reaction			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Rash generalised			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Rosacea			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Skin irritation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Dysuria			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Haematuria			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	

Anuria			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Calculus ureteric			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 78 (6.41%)	7 / 83 (8.43%)	
occurrences (all)	5	11	
Back pain			
subjects affected / exposed	5 / 78 (6.41%)	5 / 83 (6.02%)	
occurrences (all)	7	5	
Myalgia			
subjects affected / exposed	3 / 78 (3.85%)	4 / 83 (4.82%)	
occurrences (all)	3	5	
Pain in extremity			
subjects affected / exposed	3 / 78 (3.85%)	4 / 83 (4.82%)	
occurrences (all)	5	4	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 78 (2.56%)	4 / 83 (4.82%)	
occurrences (all)	2	5	
Musculoskeletal pain			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Arthritis			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Fibromyalgia			

subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Flank pain			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Bone pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Epiphyseal disorder			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Finger deformity			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Jaw disorder			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Muscle atrophy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Muscle tightness			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Synovial cyst			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Torticollis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	12 / 78 (15.38%)	19 / 83 (22.89%)	
occurrences (all)	16	26	
Nasopharyngitis			
subjects affected / exposed	10 / 78 (12.82%)	10 / 83 (12.05%)	
occurrences (all)	14	13	
Sinusitis			
subjects affected / exposed	7 / 78 (8.97%)	6 / 83 (7.23%)	
occurrences (all)	12	8	
Rhinitis			
subjects affected / exposed	4 / 78 (5.13%)	6 / 83 (7.23%)	
occurrences (all)	4	6	
Viral infection			
subjects affected / exposed	5 / 78 (6.41%)	2 / 83 (2.41%)	
occurrences (all)	5	2	
Influenza			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Pharyngitis			
subjects affected / exposed	3 / 78 (3.85%)	2 / 83 (2.41%)	
occurrences (all)	3	2	
Urinary tract infection			
subjects affected / exposed	1 / 78 (1.28%)	4 / 83 (4.82%)	
occurrences (all)	1	5	
Oral candidiasis			
subjects affected / exposed	1 / 78 (1.28%)	3 / 83 (3.61%)	
occurrences (all)	1	4	
Ear infection			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Pharyngitis streptococcal			
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)	
occurrences (all)	2	2	
Tooth infection			
subjects affected / exposed	3 / 78 (3.85%)	0 / 83 (0.00%)	
occurrences (all)	3	0	

Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 78 (1.28%)	2 / 83 (2.41%)	
occurrences (all)	1	2	
Acute sinusitis			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Bacterial disease carrier			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	2	
Laryngitis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Lung infection			
subjects affected / exposed	0 / 78 (0.00%)	2 / 83 (2.41%)	
occurrences (all)	0	6	
Respiratory tract infection viral			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Tooth abscess			
subjects affected / exposed	2 / 78 (2.56%)	0 / 83 (0.00%)	
occurrences (all)	2	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	2	
Abscess			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Bacterial infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Bronchiectasis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	

Bronchopulmonary aspergillosis				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Bronchopulmonary aspergillosis allergic				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Cellulitis				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Conjunctivitis viral				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Cystitis				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Dacryocystitis				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Diverticulitis				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Gastroenteritis viral				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Implant site infection				
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)		
occurrences (all)	1	0		
Infection				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Labyrinthitis				
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)		
occurrences (all)	0	1		
Lice infestation				

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Onychomycosis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Pancreas infection			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Pneumonia bacterial			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Pulpitis dental			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Rhinovirus infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Sputum purulent			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Staphylococcal infection			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Vaginal infection			

subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Viral pharyngitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	4 / 78 (5.13%)	3 / 83 (3.61%)	
occurrences (all)	4	3	
Decreased appetite			
subjects affected / exposed	2 / 78 (2.56%)	2 / 83 (2.41%)	
occurrences (all)	2	2	
Dehydration			
subjects affected / exposed	2 / 78 (2.56%)	1 / 83 (1.20%)	
occurrences (all)	2	2	
Hyperglycaemia			
subjects affected / exposed	1 / 78 (1.28%)	1 / 83 (1.20%)	
occurrences (all)	1	1	
Anorexia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Hypovitaminosis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 83 (0.00%)	
occurrences (all)	1	0	
Polydipsia			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 78 (0.00%)	1 / 83 (1.20%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2009	Addition of a 24-week Extension Period for a total treatment duration of 48 weeks. Change to the secondary objective to evaluate the safety of VX-770 after both 24 weeks (original objective) and 48 weeks (newly added) of treatment. Addition of a secondary objective "To evaluate the efficacy of VX-770 after 48 weeks of treatment in subjects with CF who have the G551D-CFTR mutation on at least 1 allele". Addition of a secondary endpoint of "Absolute change from baseline in percent predicted FEV1 through Week 48". Addition of analysis of secondary and tertiary endpoints at Week 48. Addition of the option for subjects who complete 48 weeks of treatment to enroll in Study VX08-770-105.
10 September 2009	Addition of the tertiary endpoint of "Pulmonary exacerbations through Weeks 24 and 48". Changed few of the inclusion/exclusion criteria. Updated the version of the CTCAE used in the study for the grading of adverse events from Version 3.0 to Version 4.0.
12 April 2010	Changes in study procedures regarding liver function testing and considerations for study drug interruption and discontinuation to ensure the continued safety of subjects in this study. Updated the name of the safety department at Vertex from "Pharmacovigilance" to "Global Patient Safety" (throughout the protocol). Updated contact information.
09 July 2010	Based on feedback from the US Food and Drug Administration (FDA), an additional criterion for removal of subjects in the study was added to protocol: total bilirubin >2 ULN and/or clinical jaundice, in association with elevation of ALT or AST >3 ULN. Additional clarification of the intended analysis were provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22047557