Clinical trial results:
A Phase 3b, Open-Label Study to Evaluate Lumacaftor and Ivacaftor Combination Therapy in Subjects 12 Years and Older With Cystic Fibrosis and Advanced Lung Disease, Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2017-001309-34
Trial protocol	Outside EU/EEA
Global end of trial date	03 October 2016

Results information

Result version number	v1 (current)
This version publication date	10 August 2017
First version publication date	10 August 2017

Trial information

Trial identification

Sponsor protocol code	VX14-809-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02390219
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2016
Global end of trial reached?	Yes
Global end of trial date	03 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of lumacaftor/ivacaftor (LUM/IVA) combination therapy in subjects 12 years and older with cystic fibrosis (CF) and advanced lung disease and who are homozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	46
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	45
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 46 subjects were enrolled and treated in the study.

Period 1

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

Arms

Arm title	LUM/IVA

Arm description:

Subjects received LUM 400 milligram (mg) in combination with IVA 250 mg as fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.

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

Dosage and administration details:

LUM 400 mg in combination with IVA 250 mg as FDC tablet q12h for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet q12h was also permitted.

Number of subjects in period 1	LUM/IVA
Started	46
Completed	33
Not completed	13
Consent withdrawn by subject	1
Physician decision	1
Death	1
Adverse event	6
Unspecified	2
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	LUM/IVA
Reporting group description:	
Subjects received LUM 400 milligram (mg) in combination with IVA 250 mg as fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.	

Reporting group values	LUM/IVA	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 32.1 ± 9	 -	
Gender categorical Units: Subjects			
Female	16	16	
Male	30	30	

End points

End points reporting groups

Reporting group title	LUM/IVA

Reporting group description:

Subjects received LUM 400 milligram (mg) in combination with IVA 250 mg as fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.

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

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs)[1]

End point description:

AE: any untoward medical occurrence in a subject during the study; event does not necessarily have a causal relationship with treatment. This includes any newly occurring event/previous condition that has increased in severity/frequency after informed consent form is signed. AE includes serious as well as non-serious AEs. SAE (subset of AE): medical event, which falls into any of the following categories, regardless of its relationship to study drug: death, life threatening adverse experience, inpatient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. TEAEs: AEs that started/ worsened on/after the start of study drug through the Safety Follow up Visit (4 weeks after the last dose of study drug). Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. Safety Set: all subjects who were exposed to any amount of study drug.

End point type	Primary

End point timeframe:

Day 1 up to Week 28

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: subjects				
Subjects with AEs	43			
Subjects with SAEs	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Up to Week 24

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Up to 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 12 to 17 years and for female subjects aged 12 to 15 years. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. Full Analysis Set (FAS) included all subjects who were enrolled and administered any amount of study drug. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Up to Week 24

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percent predicted of FEV1				
least squares mean (standard error)	-0.4 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) Up to Week 24

End point title	Absolute Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) Up to 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 FEV1 (for age, gender, race, and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 12 to 17 years and for female subjects aged 12 to 15 years. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Up to Week 24

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Litre (L)				
least squares mean (standard error)	-0.02 (± 0.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration For Which Subjects Received Intravenous (IV) Antibiotics

End point title	Duration For Which Subjects Received Intravenous (IV) Antibiotics

End point description:

The duration for which subjects received IV antibiotics for sinopulmonary signs and symptoms were reported. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here "Number of subjects analyzed" signifies those subjects who received at least one IV antibiotic for sinopulmonary signs and symptoms.

End point type	Secondary

End point timeframe:

Baseline through Week 24

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Days				
arithmetic mean (standard deviation)	11.38 (± 18.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospitalizations

End point title	Number of Hospitalizations

End point description:

Number of hospitalizations (all causes) through Week 24 was summarized. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here "Number of subjects analyzed" analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline through Week 24

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hospitalizations				
number (not applicable)	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Sweat Chloride at Average of Day 15 and Week 4

End point title	Absolute Change From Baseline in Sweat Chloride at Average of Day 15 and Week 4

End point description:

Sweat samples were collected using an approved collection device. Baseline was defined as the average of the measurements at screening and on Day 1 pre-dose. The average absolute change from baseline in sweat chloride was derived as: (Average of Day 15 and Week 4 value) minus Baseline value. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here "Number of subjects analyzed" analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 15 and Week 4

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Millimoles per litre (mmol/L)				
least squares mean (standard error)	-16.4 (± 1.3)			

Statistical analyses

No statistical analyses for this end point

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

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

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), the scaled score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:
Baseline, Through Week 24

End point values	LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Units on a scale				
least squares mean (standard error)	2.5 (± 1.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	LUM/IVA

Reporting group description:

Subjects received LUM 400 mg in combination with IVA 250 mg as FDC tablet orally q12h for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.

Serious adverse events	LUM/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 46 (39.13%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Nervous system disorders			
Neuralgia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			

subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiration abnormal				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infective pulmonary exacerbation of cystic fibrosis				
subjects affected / exposed	16 / 46 (34.78%)			
occurrences causally related to treatment / all	2 / 27			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	LUM/IVA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 46 (93.48%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	4		
Asthenia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Drug hypersensitivity			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Menorrhagia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Respiration abnormal			
subjects affected / exposed	25 / 46 (54.35%)		
occurrences (all)	39		
Cough			
subjects affected / exposed	21 / 46 (45.65%)		
occurrences (all)	32		
Dyspnoea			
subjects affected / exposed	20 / 46 (43.48%)		
occurrences (all)	28		
Sputum increased			
subjects affected / exposed	13 / 46 (28.26%)		
occurrences (all)	18		
Oropharyngeal pain			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	9		
Haemoptysis			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	10		
Nasal congestion			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	6		
Wheezing			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	7		
Respiratory tract congestion			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	4		
Upper respiratory tract congestion			

subjects affected / exposed	3 / 46 (6.52%)			
occurrences (all)	3			
Productive cough				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	3			
Rhinorrhoea				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Asthma				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Dyspnoea exertional				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Epistaxis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Increased viscosity of bronchial secretion				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Lower respiratory tract congestion				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Painful respiration				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Paranasal sinus discomfort				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Paranasal sinus hypersecretion				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Pneumothorax spontaneous				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			

Sinus congestion subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 2		
Sputum retention subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 4		
Affect lability subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Anxiety subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Depression subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Irritability subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Pulmonary function test decreased subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Blood glucose increased			

subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Blood glucose decreased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Blood immunoglobulin E increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Blood phosphorus decreased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Blood pressure diastolic increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Forced expiratory volume decreased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Fungal test positive				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Oxygen consumption increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Prostatic specific antigen increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Sputum abnormal				

subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all) White blood cell count increased subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1 1 / 46 (2.17%) 1 1 / 46 (2.17%) 1 1 / 46 (2.17%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 1 / 46 (2.17%) 2 1 / 46 (2.17%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Transient ischaemic attack subjects affected / exposed occurrences (all)	 7 / 46 (15.22%) 9 4 / 46 (8.70%) 5 2 / 46 (4.35%) 3 1 / 46 (2.17%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 1 / 46 (2.17%) 1		
Eye disorders			

Lacrimation increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Gastrointestinal tract mucosal discolouration			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		

Renal and urinary disorders			
Nephrocalcinosis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	2		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	20 / 46 (43.48%)		
occurrences (all)	26		
Nasopharyngitis			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		

Chronic sinusitis subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Clostridium difficile colitis subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Clostridium difficile infection subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Influenza subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Labyrinthitis subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Sinusitis subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Sinusitis bacterial subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Tooth abscess subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Dehydration			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2015	1. Modified eligibility criteria; 2. The Patient Health Questionnaire (PHQ) was changed from PHQ-9 to PHQ-8.
29 April 2015	1. Included additional safety precautions; 2. Text was added to reflect the option for dose modification
14 July 2015	1. Clarified that enrollment was no longer limited to subjects with ppFEV1 values greater than or equal to (>=)30 to less than (<) 40 at Screening and >=30 on Day 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported