Clinical trial results:
A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation

Summary

EudraCT number	2016-001004-33
Trial protocol	Outside EU/EEA
Global end of trial date	08 September 2017

Results information

Result version number	v1 (current)
This version publication date	07 June 2018
First version publication date	07 June 2018

Trial information

Trial identification

Sponsor protocol code	VX15-809-115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02797132
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001582-PIP01-13
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	29 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 September 2017
Global end of trial reached?	Yes
Global end of trial date	08 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) and safety of lumacaftor (LUM) and ivacaftor (IVA) combination therapy in subjects aged 2 through 5 years with cystic fibrosis (CF) homozygous for F508del

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	13 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	62
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)	62
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 2 parts, Parts A and B. In Parts A and B, subjects received LUM/IVA based on weight. Subjects in Part A could have participated in Part B.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A: LUM 100 mg/IVA 125 mg

Arm description:

Subjects weighing less than (<) 14 kilograms (kg) at screening received LUM 100 milligram (mg)/IVA 125 mg fixed-dose combination for 15 days.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA fixed-dose combination
Investigational medicinal product code	VX-809+VX-770
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered orally every 12 hours for 15 days.

Arm title	Part A: LUM 150 mg/IVA 188 mg

Arm description:

Subjects weighing greater than or equal to (>=) 14 kg at screening received LUM 150 mg/IVA 188 mg fixed-dose combination for 15 days.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA fixed-dose combination
Investigational medicinal product code	VX-809+VX-770
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered orally every 12 hours for 15 days.

Arm title	Part B: LUM 100 mg/IVA 125 mg

Arm description:

Subjects weighing less than <14 kg at screening received LUM 100 mg/IVA 125 mg fixed-dose combination for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA fixed-dose combination
Investigational medicinal product code	VX-809+VX-770
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered orally every 12 hours for 24 weeks.

Arm title	Part B: LUM 150 mg/IVA 188 mg

Arm description:

Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg fixed-dose combination for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA fixed-dose combination
Investigational medicinal product code	VX-809+VX-770
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Administered orally every 12 hours 24 weeks.

Number of subjects in period 1	Part A: LUM 100 mg/IVA 125 mg	Part A: LUM 150 mg/IVA 188 mg	Part B: LUM 100 mg/IVA 125 mg
Started	4	8	19
Completed	4	7	19
Not completed	0	1	0
Adverse Event	-	1	-

Number of subjects in period 1	Part B: LUM 150 mg/IVA 188 mg
Started	41
Completed	38
Not completed	3
Adverse Event	3

Baseline characteristics

Reporting groups	
Reporting group title	Part A: LUM 100 mg/IVA 125 mg
Reporting group description:	
Subjects weighing less than (<) 14 kilograms (kg) at screening received LUM 100 milligram (mg)/IVA 125 mg fixed-dose combination for 15 days.	
Reporting group title	Part A: LUM 150 mg/IVA 188 mg
Reporting group description:	
Subjects weighing greater than or equal to (>=) 14 kg at screening received LUM 150 mg/IVA 188 mg fixed-dose combination for 15 days.	
Reporting group title	Part B: LUM 100 mg/IVA 125 mg
Reporting group description:	
Subjects weighing less than <14 kg at screening received LUM 100 mg/IVA 125 mg fixed-dose combination for 24 weeks.	
Reporting group title	Part B: LUM 150 mg/IVA 188 mg
Reporting group description:	
Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg fixed-dose combination for 24 weeks.	

Reporting group values	Part A: LUM 100 mg/IVA 125 mg	Part A: LUM 150 mg/IVA 188 mg	Part B: LUM 100 mg/IVA 125 mg
Number of subjects	4	8	19
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean	27	48	31.6
standard deviation	± 6	± 11.11	± 5.05
Gender categorical			
Units: Subjects			
Female	2	2	9
Male	2	6	10

Reporting group values	Part B: LUM 150 mg/IVA 188 mg	Total	
Number of subjects	41	72	
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean	49.9		
standard deviation	± 10.63	-	
Gender categorical			
Units: Subjects			
Female	20	33	
Male	21	39	

End points

End points reporting groups

Reporting group title	Part A: LUM 100 mg/IVA 125 mg
Reporting group description:	
Subjects weighing less than (<) 14 kilograms (kg) at screening received LUM 100 milligram (mg)/IVA 125 mg fixed-dose combination for 15 days.	
Reporting group title	Part A: LUM 150 mg/IVA 188 mg
Reporting group description:	
Subjects weighing greater than or equal to (>=) 14 kg at screening received LUM 150 mg/IVA 188 mg fixed-dose combination for 15 days.	
Reporting group title	Part B: LUM 100 mg/IVA 125 mg
Reporting group description:	
Subjects weighing less than <14 kg at screening received LUM 100 mg/IVA 125 mg fixed-dose combination for 24 weeks.	
Reporting group title	Part B: LUM 150 mg/IVA 188 mg
Reporting group description:	
Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg fixed-dose combination for 24 weeks.	

Primary: Part A: Pre-dose Concentration (Ctrough) of Lumacaftor (LUM) and Ivacaftor (IVA)

End point title	Part A: Pre-dose Concentration (Ctrough) of Lumacaftor (LUM) and Ivacaftor (IVA)[1][2]
End point description:	
End point type	Primary
End point timeframe:	
Day 15	

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: No statistical testing was planned for this endpoint. Therefore, only descriptive data is provided.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This primary endpoint is only applicable for Part A. Therefore, only Part A arms are included here.

End point values	Part A: LUM 100 mg/IVA 125 mg	Part A: LUM 150 mg/IVA 188 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
LUM	8710 (± 3590)	12300 (± 5960)		
IVA	94.0 (± 67.0)	216 (± 185)		

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part B: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[3][4]

End point description:

End point type	Primary

End point timeframe:

Day 1 up to Week 26

Notes:

[3] - 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: No statistical testing was planned for this endpoint. Therefore, only descriptive data is provided.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This primary endpoint for AEs is only applicable for Part B. Therefore, only Part B arms are included here.

End point values	Part B: LUM 100 mg/IVA 125 mg	Part B: LUM 150 mg/IVA 188 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	41		
Units: subjects				
AEs	19	40		
SAEs	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Part A: Day 1 up to Day 25; Part B: Day 1 up to Week 26	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Part A: LUM 100 mg/IVA 125 mg
Reporting group description: -	
Reporting group title	Part B: LUM 100 mg/IVA 125 mg
Reporting group description: -	
Reporting group title	Part B: LUM 150 mg/IVA 188 mg
Reporting group description: -	
Reporting group title	Part A: LUM 150 mg/IVA 188 mg
Reporting group description: -	

Serious adverse events	Part A: LUM 100 mg/IVA 125 mg	Part B: LUM 100 mg/IVA 125 mg	Part B: LUM 150 mg/IVA 188 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	2 / 41 (4.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A: LUM 150 mg/IVA 188 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A: LUM 100 mg/IVA 125 mg	Part B: LUM 100 mg/IVA 125 mg	Part B: LUM 150 mg/IVA 188 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	19 / 19 (100.00%)	40 / 41 (97.56%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	7 / 19 (36.84%)	10 / 41 (24.39%)
occurrences (all)	0	9	12
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Chills			

subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 4 (50.00%)	12 / 19 (63.16%)	26 / 41 (63.41%)
occurrences (all)	3	23	52
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	8 / 19 (42.11%)	7 / 41 (17.07%)
occurrences (all)	0	9	13
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)	4 / 19 (21.05%)	6 / 41 (14.63%)
occurrences (all)	1	4	9
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	3 / 41 (7.32%)
occurrences (all)	0	1	3
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Nasal discharge discolouration			

subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	2 / 41 (4.88%)
occurrences (all)	0	2	2
Wheezing			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	2 / 41 (4.88%)
occurrences (all)	0	2	2
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Respiration abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Sputum discoloured			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Tonsillar inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Psychiatric disorders			
Enuresis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Sleep terror			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Tearfulness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Investigations			
Respiratory rate increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	5 / 41 (12.20%)
occurrences (all)	0	3	5
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	4 / 41 (9.76%)
occurrences (all)	0	2	4
Forced expiratory volume decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Pseudomonas test positive			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	2 / 41 (4.88%)
occurrences (all)	0	3	2
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Burkholderia test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
International normalised ratio increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Prothrombin time prolonged			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Pulmonary function test decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1

Staphylococcus test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Streptococcus test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Bacterial test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood iron decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Enterovirus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Respirovirus test positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Vitamin D decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Radial head dislocation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	4 / 41 (9.76%)
occurrences (all)	0	0	6
Cognitive disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Lymphocytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Lacrimation increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Faeces discoloured			
subjects affected / exposed	1 / 4 (25.00%)	0 / 19 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Faeces soft			
subjects affected / exposed	2 / 4 (50.00%)	0 / 19 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0

Flatulence			
subjects affected / exposed	1 / 4 (25.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	6 / 19 (31.58%)	11 / 41 (26.83%)
occurrences (all)	2	7	13
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	4 / 41 (9.76%)
occurrences (all)	0	4	5
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	4 / 41 (9.76%)
occurrences (all)	0	2	4
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	3 / 41 (7.32%)
occurrences (all)	0	1	3
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Oral discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Post-tussive vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Steatorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	1 / 41 (2.44%)
occurrences (all)	0	2	1

Dyschezia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Frequent bowel movements			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	1 / 41 (2.44%)
occurrences (all)	0	3	1
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 19 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	3
Lice infestation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	7 / 41 (17.07%)
occurrences (all)	0	4	12
Ear infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	4 / 41 (9.76%)
occurrences (all)	0	5	6
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	4 / 41 (9.76%)
occurrences (all)	0	0	5
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	3 / 41 (7.32%)
occurrences (all)	0	3	4
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	2 / 41 (4.88%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	2 / 41 (4.88%)
occurrences (all)	0	1	2
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	2 / 41 (4.88%)
occurrences (all)	0	2	4
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Impetigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Labyrinthitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	1 / 41 (2.44%)
occurrences (all)	0	2	1
Viral rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 19 (0.00%)	1 / 41 (2.44%)
occurrences (all)	0	0	1
Candida nappy rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	2 / 41 (4.88%)
occurrences (all)	0	1	3
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	1 / 41 (2.44%)
occurrences (all)	0	2	1

Non-serious adverse events	Part A: LUM 150 mg/IVA 188 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nasal discharge discolouration			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiration abnormal			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Sputum discoloured			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Tonsillar inflammation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Upper respiratory tract congestion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Enuresis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Sleep terror			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Tearfulness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Investigations			
Respiratory rate increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Forced expiratory volume decreased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pseudomonas test positive			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Burkholderia test positive				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
International normalised ratio increased				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Prothrombin time prolonged				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Pulmonary function test decreased				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Staphylococcus test positive				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Streptococcus test positive				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Bacterial test positive				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Blood iron decreased				

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Enterovirus test positive			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respirovirus test positive			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Radial head dislocation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cognitive disorder			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lymphocytosis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Faeces discoloured			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Faeces soft			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nausea			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Oral discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Post-tussive vomiting			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Steatorrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dyschezia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Frequent bowel movements			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Eczema			

subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all) Lice infestation subjects affected / exposed occurrences (all) Lower respiratory tract infection viral subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		

Upper respiratory tract infection				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Ear infection				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Conjunctivitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Cellulitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Impetigo				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Labyrinthitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Pharyngitis streptococcal				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Viral rash				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Candida nappy rash subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Gastroenteritis rotavirus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Dehydration subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2016	- Added a Washout Period - Removed inclusion criterion related to ppFEV1
13 April 2017	- Included prescription for a short-acting bronchodilator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported