Clinical trial results:
A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2015-001644-11
Trial protocol	SE GB BE DK DE FR
Global end of trial date	24 April 2020

Results information

Result version number	v1
This version publication date	06 November 2020
First version publication date	06 November 2020

Trial information

Trial identification

Sponsor protocol code	VX15-809-110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02544451
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
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	14 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2018
Global end of trial reached?	Yes
Global end of trial date	24 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term safety and tolerability of lumacaftor (LUM) in combination with ivacaftor (IVA) in subjects aged 6 years and older with cystic fibrosis (CF), homozygous for the F508del CFTR mutation, who are in the Treatment Cohort.

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 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 143
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Australia: 28
Worldwide total number of subjects	246
EEA total number of subjects	54

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	225
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study consists of 2 Treatment Periods: Treatment Period 1 and Treatment Period 2. Treatment Period 1 had a Treatment Cohort and an Observational Cohort.

Pre-assignment

Screening details:

Subjects from Parent Studies 109 (NCT02514473) and 011B (NCT01897233) were enrolled in this study. A total of 240 subjects were enrolled in Treatment Cohort, out of which 1 subject was enrolled but never dosed. Subjects enrolled in the Observational Cohort were followed for safety endpoints only, no efficacy data were collected.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LUM/IVA to LUM/IVA

Arm description:

Subjects received LUM/IVA in parent studies (109, 011B) and continued to receive LUM/IVA for 96 weeks in the current study.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	VX-809/VX-770
Other name	lumacaftor/ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received LUM/IVA twice daily for 96 weeks.

Arm title	PBO to LUM/IVA

Arm description:

Subjects received placebo (PBO) in parent study (109) and then received LUM/IVA for 96 weeks in the current study.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	VX-809/VX-770
Other name	lumacaftor/ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received LUM/IVA twice daily for 96 weeks.

Arm title	Observational Cohort

Arm description:

Subjects completed a parent study (109, 011B) but were not eligible or elected to not receive LUM/IVA for 96 weeks in the current study.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	LUM/IVA to LUM/IVA	PBO to LUM/IVA	Observational Cohort
Started	143	96	6
Completed	129	84	5
Not completed	14	12	1
Physician decision	4	-	-
Adverse Event	1	6	-
Other	4	4	-
Withdrawal of consent	-	-	1
Lost to follow-up	2	-	-
Withdrawal of consent (not due to AE)	3	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 240 subjects were enrolled in Treatment Cohort of Treatment Period 1, out of which 1 subject was enrolled but never dosed.

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LUM/IVA

Arm description:

Eligible subjects from Treatment Period 1 received LUM/IVA for up to approximately 168 weeks.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	VX-809/VX-770
Other name	lumacaftor/ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received LUM/IVA twice daily for 168 weeks.

Number of subjects in period 2[2]	LUM/IVA
Started	10
Completed	0
Not completed	10
Commercial drug is available for subject	10

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only eligible subjects from Treatment Period 1 received LUM/IVA during optional Treatment Period 2.

Baseline characteristics

Reporting groups	
Reporting group title	LUM/IVA to LUM/IVA
Reporting group description:	
Subjects received LUM/IVA in parent studies (109, 011B) and continued to receive LUM/IVA for 96 weeks in the current study.	
Reporting group title	PBO to LUM/IVA
Reporting group description:	
Subjects received placebo (PBO) in parent study (109) and then received LUM/IVA for 96 weeks in the current study.	
Reporting group title	Observational Cohort
Reporting group description:	
Subjects completed a parent study (109, 011B) but were not eligible or elected to not receive LUM/IVA for 96 weeks in the current study.	

Reporting group values	LUM/IVA to LUM/IVA	PBO to LUM/IVA	Observational Cohort
Number of subjects	143	96	6
Age categorical Units: Subjects			
Less than 9 Years	58	38	5
Greater than or equal to 9 years	85	58	1
Gender categorical Units: Subjects			
Female	83	56	2
Male	60	40	4

Reporting group values	Total		
Number of subjects	245		
Age categorical Units: Subjects			
Less than 9 Years	101		
Greater than or equal to 9 years	144		
Gender categorical Units: Subjects			
Female	141		
Male	104		

End points

End points reporting groups

Reporting group title	LUM/IVA to LUM/IVA
Reporting group description:	
Subjects received LUM/IVA in parent studies (109, 011B) and continued to receive LUM/IVA for 96 weeks in the current study.	
Reporting group title	PBO to LUM/IVA
Reporting group description:	
Subjects received placebo (PBO) in parent study (109) and then received LUM/IVA for 96 weeks in the current study.	
Reporting group title	Observational Cohort
Reporting group description:	
Subjects completed a parent study (109, 011B) but were not eligible or elected to not receive LUM/IVA for 96 weeks in the current study.	
Reporting group title	LUM/IVA
Reporting group description:	
Eligible subjects from Treatment Period 1 received LUM/IVA for up to approximately 168 weeks.	

Primary: Treatment Period 1 (Treatment Cohort): Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Treatment Period 1 (Treatment Cohort): Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[1][2]
End point description:	
Safety set included all participants who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Day 1 up to Week 100	

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 analyses were planned for this endpoint. Therefore, only descriptive data are 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 endpoint was applicable for Treatment Period 1 Treatment cohort arms. Therefore, data are reported for these arms only.

End point values	LUM/IVA to LUM/IVA	PBO to LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	96		
Units: subjects				
Subjects with any AEs	142	94		
Subjects with SAEs	43	29		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Period 1: Day 1 up to Week 100
Treatment Period 2: Day 1 up to Week 168

Adverse event reporting additional description:

Only serious adverse events were collected for the observational cohort. Non-serious AEs were not collected and are not reported for the observational cohort.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0, 22.1

Reporting groups

Reporting group title	Treatment Period 1: LUM/IVA to LUM/IVA

Reporting group description:

Subjects received LUM/IVA in parent studies (109, 011B) and continued to receive LUM/IVA for 96 weeks in the current study.

Reporting group title	Treatment Period 1: PBO to LUM/IVA

Reporting group description:

Subjects received placebo (PBO) in parent study (109) and then received LUM/IVA for 96 weeks in the current study.

Reporting group title	Observational Cohort

Reporting group description:

Subjects completed a parent study (109, 011B) but were not eligible or elected to not receive LUM/IVA for 96 weeks in the current study.

Reporting group title	Treatment Period 2: LUM/IVA

Reporting group description:

Eligible subjects from Treatment Period 1 received LUM/IVA for up to approximately 168 weeks.

Serious adverse events	Treatment Period 1: LUM/IVA to LUM/IVA	Treatment Period 1: PBO to LUM/IVA	Observational Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 143 (30.07%)	29 / 96 (30.21%)	1 / 6 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	2 / 143 (1.40%)	2 / 96 (2.08%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterium test positive			

subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas test positive			
subjects affected / exposed	1 / 143 (0.70%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 143 (0.00%)	2 / 96 (2.08%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 143 (0.00%)	2 / 96 (2.08%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cystic fibrosis hepatic disease			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Cystic fibrosis lung			

subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 143 (2.80%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			

subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus disorder			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	34 / 143 (23.78%)	15 / 96 (15.63%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 48	1 / 25	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	2 / 143 (1.40%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection bacterial			

subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (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

Serious adverse events	Treatment Period 2: LUM/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Investigations			
Pulmonary function test decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atypical mycobacterium test positive			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonas test positive			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cystic fibrosis hepatic disease			

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystic fibrosis lung				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Lymphadenitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Constipation				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Distal intestinal obstruction syndrome				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Autoimmune hepatitis				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus disorder			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 10 (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 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atypical mycobacterial lower respiratory tract infection			

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection bacterial				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetic ketoacidosis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 10 (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: 5 %

Non-serious adverse events	Treatment Period 1: LUM/IVA to LUM/IVA	Treatment Period 1: PBO to LUM/IVA	Observational Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 143 (98.60%)	93 / 96 (96.88%)	0 / 6 (0.00%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	45 / 143 (31.47%)	27 / 96 (28.13%)	0 / 6 (0.00%)
occurrences (all)	64	41	0
Fatigue			
subjects affected / exposed	10 / 143 (6.99%)	11 / 96 (11.46%)	0 / 6 (0.00%)
occurrences (all)	14	12	0
Chest pain			
subjects affected / exposed	2 / 143 (1.40%)	5 / 96 (5.21%)	0 / 6 (0.00%)
occurrences (all)	2	5	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	8 / 143 (5.59%)	5 / 96 (5.21%)	0 / 6 (0.00%)
occurrences (all)	13	6	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	91 / 143 (63.64%)	64 / 96 (66.67%)	0 / 6 (0.00%)
occurrences (all)	195	166	0
Nasal congestion			
subjects affected / exposed	34 / 143 (23.78%)	21 / 96 (21.88%)	0 / 6 (0.00%)
occurrences (all)	60	29	0
Oropharyngeal pain			
subjects affected / exposed	32 / 143 (22.38%)	18 / 96 (18.75%)	0 / 6 (0.00%)
occurrences (all)	59	29	0
Rhinorrhoea			
subjects affected / exposed	24 / 143 (16.78%)	13 / 96 (13.54%)	0 / 6 (0.00%)
occurrences (all)	39	18	0
Productive cough			
subjects affected / exposed	19 / 143 (13.29%)	15 / 96 (15.63%)	0 / 6 (0.00%)
occurrences (all)	51	26	0

Sputum increased			
subjects affected / exposed	18 / 143 (12.59%)	7 / 96 (7.29%)	0 / 6 (0.00%)
occurrences (all)	21	7	0
Sinus congestion			
subjects affected / exposed	12 / 143 (8.39%)	4 / 96 (4.17%)	0 / 6 (0.00%)
occurrences (all)	16	5	0
Nasal polyps			
subjects affected / exposed	9 / 143 (6.29%)	3 / 96 (3.13%)	0 / 6 (0.00%)
occurrences (all)	9	4	0
Haemoptysis			
subjects affected / exposed	8 / 143 (5.59%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	10	1	0
Wheezing			
subjects affected / exposed	8 / 143 (5.59%)	4 / 96 (4.17%)	0 / 6 (0.00%)
occurrences (all)	9	6	0
Respiration abnormal			
subjects affected / exposed	7 / 143 (4.90%)	7 / 96 (7.29%)	0 / 6 (0.00%)
occurrences (all)	7	8	0
Asthma			
subjects affected / exposed	5 / 143 (3.50%)	5 / 96 (5.21%)	0 / 6 (0.00%)
occurrences (all)	6	5	0
Dyspnoea			
subjects affected / exposed	4 / 143 (2.80%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	4	6	0
Bronchiectasis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	5 / 143 (3.50%)	2 / 96 (2.08%)	0 / 6 (0.00%)
occurrences (all)	5	2	0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 143 (0.70%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Paranasal sinus hypersecretion			
subjects affected / exposed	4 / 143 (2.80%)	2 / 96 (2.08%)	0 / 6 (0.00%)
occurrences (all)	4	2	0

Rales			
subjects affected / exposed	2 / 143 (1.40%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Rhinitis allergic			
subjects affected / exposed	4 / 143 (2.80%)	4 / 96 (4.17%)	0 / 6 (0.00%)
occurrences (all)	4	4	0
Investigations			
Bacterial test positive			
subjects affected / exposed	30 / 143 (20.98%)	16 / 96 (16.67%)	0 / 6 (0.00%)
occurrences (all)	45	46	0
Alanine aminotransferase increased			
subjects affected / exposed	22 / 143 (15.38%)	21 / 96 (21.88%)	0 / 6 (0.00%)
occurrences (all)	27	26	0
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 143 (11.89%)	13 / 96 (13.54%)	0 / 6 (0.00%)
occurrences (all)	22	16	0
Pseudomonas test positive			
subjects affected / exposed	10 / 143 (6.99%)	3 / 96 (3.13%)	0 / 6 (0.00%)
occurrences (all)	10	6	0
Pulmonary function test decreased			
subjects affected / exposed	8 / 143 (5.59%)	11 / 96 (11.46%)	0 / 6 (0.00%)
occurrences (all)	9	11	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	6 / 143 (4.20%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	6	7	0
Forced expiratory volume decreased			
subjects affected / exposed	6 / 143 (4.20%)	13 / 96 (13.54%)	0 / 6 (0.00%)
occurrences (all)	8	16	0
International normalised ratio increased			
subjects affected / exposed	4 / 143 (2.80%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	5	6	0
Prothrombin time prolonged			
subjects affected / exposed	3 / 143 (2.10%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	4	7	0
Weight decreased			

subjects affected / exposed	1 / 143 (0.70%)	5 / 96 (5.21%)	0 / 6 (0.00%)
occurrences (all)	1	5	0
Pulmonary imaging procedure abnormal			
subjects affected / exposed	0 / 143 (0.00%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	4 / 143 (2.80%)	2 / 96 (2.08%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 143 (20.28%)	26 / 96 (27.08%)	0 / 6 (0.00%)
occurrences (all)	43	36	0
Dizziness			
subjects affected / exposed	6 / 143 (4.20%)	5 / 96 (5.21%)	0 / 6 (0.00%)
occurrences (all)	7	6	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	12 / 143 (8.39%)	4 / 96 (4.17%)	0 / 6 (0.00%)
occurrences (all)	17	5	0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 143 (0.00%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	30 / 143 (20.98%)	15 / 96 (15.63%)	0 / 6 (0.00%)
occurrences (all)	36	18	0
Abdominal pain upper			
subjects affected / exposed	22 / 143 (15.38%)	20 / 96 (20.83%)	0 / 6 (0.00%)
occurrences (all)	38	30	0
Abdominal pain			
subjects affected / exposed	17 / 143 (11.89%)	19 / 96 (19.79%)	0 / 6 (0.00%)
occurrences (all)	23	24	0
Diarrhoea			

subjects affected / exposed	16 / 143 (11.19%)	8 / 96 (8.33%)	0 / 6 (0.00%)
occurrences (all)	16	10	0
Nausea			
subjects affected / exposed	13 / 143 (9.09%)	11 / 96 (11.46%)	0 / 6 (0.00%)
occurrences (all)	15	15	0
Constipation			
subjects affected / exposed	11 / 143 (7.69%)	11 / 96 (11.46%)	0 / 6 (0.00%)
occurrences (all)	13	14	0
Flatulence			
subjects affected / exposed	4 / 143 (2.80%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	4	8	0
Dyspepsia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 143 (0.70%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	10 / 143 (6.99%)	10 / 96 (10.42%)	0 / 6 (0.00%)
occurrences (all)	12	11	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 143 (3.50%)	5 / 96 (5.21%)	0 / 6 (0.00%)
occurrences (all)	6	5	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	59 / 143 (41.26%)	34 / 96 (35.42%)	0 / 6 (0.00%)
occurrences (all)	115	70	0
Upper respiratory tract infection			
subjects affected / exposed	36 / 143 (25.17%)	13 / 96 (13.54%)	0 / 6 (0.00%)
occurrences (all)	52	21	0

Nasopharyngitis			
subjects affected / exposed	21 / 143 (14.69%)	16 / 96 (16.67%)	0 / 6 (0.00%)
occurrences (all)	34	29	0
Viral upper respiratory tract infection			
subjects affected / exposed	21 / 143 (14.69%)	14 / 96 (14.58%)	0 / 6 (0.00%)
occurrences (all)	28	20	0
Sinusitis			
subjects affected / exposed	17 / 143 (11.89%)	8 / 96 (8.33%)	0 / 6 (0.00%)
occurrences (all)	19	9	0
Otitis media			
subjects affected / exposed	13 / 143 (9.09%)	8 / 96 (8.33%)	0 / 6 (0.00%)
occurrences (all)	13	10	0
Pharyngitis streptococcal			
subjects affected / exposed	12 / 143 (8.39%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	23	6	0
Bacterial disease carrier			
subjects affected / exposed	11 / 143 (7.69%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	15	8	0
Influenza			
subjects affected / exposed	11 / 143 (7.69%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	16	7	0
Ear infection			
subjects affected / exposed	9 / 143 (6.29%)	7 / 96 (7.29%)	0 / 6 (0.00%)
occurrences (all)	10	10	0
Rhinitis			
subjects affected / exposed	9 / 143 (6.29%)	7 / 96 (7.29%)	0 / 6 (0.00%)
occurrences (all)	19	10	0
Upper respiratory tract infection bacterial			
subjects affected / exposed	8 / 143 (5.59%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	9	1	0
Bronchitis			
subjects affected / exposed	7 / 143 (4.90%)	7 / 96 (7.29%)	0 / 6 (0.00%)
occurrences (all)	10	9	0
Pharyngitis			

subjects affected / exposed	5 / 143 (3.50%)	7 / 96 (7.29%)	0 / 6 (0.00%)
occurrences (all)	5	12	0
Gastroenteritis			
subjects affected / exposed	7 / 143 (4.90%)	4 / 96 (4.17%)	0 / 6 (0.00%)
occurrences (all)	8	4	0
Oral fungal infection			
subjects affected / exposed	2 / 143 (1.40%)	0 / 96 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection bacterial			
subjects affected / exposed	3 / 143 (2.10%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 143 (2.10%)	6 / 96 (6.25%)	0 / 6 (0.00%)
occurrences (all)	5	6	0
Glucose tolerance impaired			
subjects affected / exposed	1 / 143 (0.70%)	1 / 96 (1.04%)	0 / 6 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Treatment Period 2: LUM/IVA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Sputum increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nasal polyps			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiration abnormal			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Asthma			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Bronchiectasis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Lower respiratory tract congestion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Rales			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Investigations			
Bacterial test positive			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pseudomonas test positive			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pulmonary function test decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Forced expiratory volume decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Prothrombin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pulmonary imaging procedure abnormal			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hepatobiliary disorders			

Hepatomegaly subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 6		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Sinusitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Otitis media subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Bacterial disease carrier subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		

Influenza subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Ear infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Rhinitis subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 11		
Upper respiratory tract infection bacterial subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Bronchitis subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Pharyngitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Oral fungal infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Respiratory tract infection bacterial subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Glucose tolerance impaired subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2015	Amended to assess post-dose spirometry.
30 November 2017	Amended to add Treatment Period 2 to assess long-term safety of LUM/IVA in subjects who completed 96 weeks of LUM/IVA treatment in Treatment Period 1.
16 May 2019	Amended to extend Treatment Cohort Period 2 for up to an additional 96 weeks (up to a total of 264 weeks of treatment).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported