Clinical trial results:
An Exploratory Phase 2, 2-part, Randomized, Double blind, Placebo controlled Study With a Long term, Open label Period to Explore the Impact of Lumacaftor/Ivacaftor on Disease Progression in Subjects Aged 2 Through 5 Years With Cystic Fibrosis, Homozygous for F508del

Summary

EudraCT number	2017-003761-99
Trial protocol	DE
Global end of trial date	07 October 2021

Results information

Result version number	v1 (current)
This version publication date	22 April 2022
First version publication date	22 April 2022

Trial information

Trial identification

Sponsor protocol code	VX16-809-121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03625466
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)	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	03 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2020
Global end of trial reached?	Yes
Global end of trial date	07 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the impact of lumacaftor (LUM)/ivacaftor (IVA) on disease progression 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 Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2018
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	Germany: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	51
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:

This study was planned in 2 parts: Part 1 (Placebo-controlled Period) and Part 2 (Open-label Period). The primary and secondary efficacy analyses were planned for only Part 1.

Pre-assignment

Screening details:

This study was conducted in subjects with CF aged 2 to 5 years.

Period 1

Period 1 title	Placebo-controlled Period (48 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Placebo

Arm description:

Subjects received placebo matched to LUM/IVA in placebo-controlled period for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to LUM/IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to LUM/IVA twice daily.

Arm title	Part 1: LUM/IVA

Arm description:

Subjects weighing less than (<)14 kilograms (kg) at screening received LUM 100 milligrams (mg)/IVA 125 mg fixed-dose combination (FDC) every 12 hours (q12h) in placebo-controlled period for 48 weeks. Subjects weighing greater than or equals to (>=)14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h in placebo-controlled period for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	VX-809/VX-770
Other name	Lumacaftor/Ivacaftor
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received LUM/IVA FDC twice daily.

Number of subjects in period 1	Part 1: Placebo	Part 1: LUM/IVA
Started	16	35
Completed	16	33
Not completed	0	2
Adverse Event	-	1
Withdrawal of Consent (not due to AE)	-	1

Period 2

Period 2 title	Open-label Period (48 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part 2: Overall LUM/IVA

Arm description:

Subjects who received either placebo or LUM/IVA in placebo-controlled period administered LUM/IVA (either LUM 100 mg/IVA 125 mg FDC q12h or LUM 150 mg/IVA 188 mg FDC q12h as per their body weight for subjects <6 years of age at week 48 and LUM 200 mg/IVA 250 mg FDC q12h regardless of their body weight for subjects >=6 years of age at week 48) in open-label period for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	LUM/IVA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received LUM/IVA FDC twice daily.

Number of subjects in period 2	Part 2: Overall LUM/IVA
Started	49
Completed	48
Not completed	1
Withdrawal of Consent (not due to AE)	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Placebo
Reporting group description:	
Subjects received placebo matched to LUM/IVA in placebo-controlled period for 48 weeks.	
Reporting group title	Part 1: LUM/IVA
Reporting group description:	
Subjects weighing less than (<)14 kilograms (kg) at screening received LUM 100 milligrams (mg)/IVA 125 mg fixed-dose combination (FDC) every 12 hours (q12h) in placebo-controlled period for 48 weeks. Subjects weighing greater than or equals to (>=)14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h in placebo-controlled period for 48 weeks.	

Reporting group values	Part 1: Placebo	Part 1: LUM/IVA	Total
Number of subjects	16	35	51
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	4.2	4.2	
standard deviation	± 1.0	± 1.0	-
Gender categorical			
Units: Subjects			
Female	7	11	18
Male	9	24	33
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	16	35	51
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	16	35	51
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Part 1: Placebo
Reporting group description:	
Subjects received placebo matched to LUM/IVA in placebo-controlled period for 48 weeks.	

Reporting group title	Part 1: LUM/IVA
Reporting group description:	
Subjects weighing less than (<)14 kilograms (kg) at screening received LUM 100 milligrams (mg)/IVA 125 mg fixed-dose combination (FDC) every 12 hours (q12h) in placebo-controlled period for 48 weeks. Subjects weighing greater than or equals to (>=)14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h in placebo-controlled period for 48 weeks.	

Reporting group title	Part 2: Overall LUM/IVA
Reporting group description:	
Subjects who received either placebo or LUM/IVA in placebo-controlled period administered LUM/IVA (either LUM 100 mg/IVA 125 mg FDC q12h or LUM 150 mg/IVA 188 mg FDC q12h as per their body weight for subjects <6 years of age at week 48 and LUM 200 mg/IVA 250 mg FDC q12h regardless of their body weight for subjects >=6 years of age at week 48) in open-label period for 48 weeks.	

Primary: Part 1: Absolute Change From Baseline in Magnetic Resonance Imaging (MRI) Global Chest Score at Week 48

End point title	Part 1: Absolute Change From Baseline in Magnetic Resonance Imaging (MRI) Global Chest Score at Week 48
End point description:	
MRI scans assessed semi-quantitatively via a standardized chest MRI scoring system. Each subject had 6 lobes scored using 7 scoring parameters:1) Bronchiectasis/wall thickening 2) Mucus plugging 3) Abscesses/sacculations 4) Consolidations 5) Special findings 6)Mosaic pattern 7) Perfusion abnormalities. For each of 7 parameter, there were scores of 6 lobes (score of each lobe : 0= normal value, 1 = <50% of lobe involved and 2 = >=50% of lobe involved). MRI global score was calculated as sum of parameters 1 to 7. MRI total score is ranged from 0-84. Higher score indicate more lobe involvement. Full Analysis Set (FAS) included all randomized subjects who carried the intended CF transmembrane conductance regulator gene (CFTR) allele mutation and received at least 1 dose of study drug in Part 1.Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.	
End point type	Primary
End point timeframe:	
From Baseline at Week 48	

End point values	Part 1: Placebo	Part 1: LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	35		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=15,34)	21.4 (± 9.3)	17.6 (± 9.7)		
Change at Week 48 (n=15,32)	-0.3 (± 6.1)	-1.7 (± 6.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part 1: Placebo v Part 1: LUM/IVA
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	2.6

Secondary: Part 1: Absolute Change in Lung Clearance Index2.5 (LCI2.5) Through Week 48

End point title	Part 1: Absolute Change in Lung Clearance Index2.5 (LCI2.5) Through Week 48

End point description:

LCI2.5 represents the number of lung turnovers required to reduce the end-tidal inert gas concentration to 1/40th of its starting value. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 48

End point values	Part 1: Placebo	Part 1: LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	35		
Units: lung clearance index				
arithmetic mean (confidence interval 95%)	0.32 (-0.20 to 0.84)	-0.37 (-0.85 to 0.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Absolute Change in Weight-for-age Z-score at Week 48

End point title	Part 1: Absolute Change in Weight-for-age Z-score at Week 48

End point description:

The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. FAS.

End point type	Secondary

End point timeframe:

From Baseline at Week 48

End point values	Part 1: Placebo	Part 1: LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	35		
Units: z-score				
arithmetic mean (confidence interval 95%)	-0.07 (-0.24 to 0.11)	0.13 (-0.01 to 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Absolute Change in Stature-for-age Z-score at Week 48

End point title	Part 1: Absolute Change in Stature-for-age Z-score at Week 48

End point description:

The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. FAS.

End point type	Secondary

End point timeframe:

From Baseline at Week 48

End point values	Part 1: Placebo	Part 1: LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	35		
Units: z-score				
arithmetic mean (confidence interval 95%)	0.10 (-0.04 to 0.24)	0.09 (-0.05 to 0.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Absolute Change in Body Mass Index (BMI)-For-age Z-score at Week 48

End point title	Part 1: Absolute Change in Body Mass Index (BMI)-For-age Z-score at Week 48

End point description:

BMI was defined as weight in kilogram (kg) divided by squared height in meters (m^2). The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal

to the standard. Lower numbers indicate values lower than the standard and higher numbers indicate values higher than the standard. FAS.

End point type	Secondary

End point timeframe:

From Baseline at Week 48

End point values	Part 1: Placebo	Part 1: LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	35		
Units: z-score				
arithmetic mean (confidence interval 95%)	-0.24 (-0.55 to 0.07)	0.20 (-0.02 to 0.41)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to Week 98 (Part 1: From Day 1 up to Week 48; Part 2: From Week 48 up to Week 98)

Adverse event reporting additional description:

MedDRA 23.1 applied for Part 1 and MedDRA 24.0 applied for Part 2.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1, 24.0

Reporting groups

Reporting group title	Part 1: Placebo

Reporting group description:

Subjects received placebo matched to LUM/IVA in placebo-controlled period for 48 weeks.

Reporting group title	Part 1: LUM/IVA

Reporting group description:

Subjects weighing <14 kg at screening received LUM 100 mg/IVA 125 mg FDC q12h in placebo-controlled period for 48 weeks. Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h in placebo-controlled period for 48 weeks.

Reporting group title	Part 2: Overall LUM/IVA

Reporting group description:

Subjects who received either placebo or LUM/IVA in placebo-controlled period administered LUM/IVA (either LUM 100 mg/IVA 125 mg FDC q12h or LUM 150 mg/IVA 188 mg FDC q12h as per their body weight for subjects <6 years of age at week 48 and LUM 200 mg/IVA 250 mg FDC q12h regardless of their body weight for subjects >=6 years of age at week 48) in open-label period for 48 weeks.

Serious adverse events	Part 1: Placebo	Part 1: LUM/IVA	Part 2: Overall LUM/IVA
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	7 / 35 (20.00%)	12 / 49 (24.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Sedation complication			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	2 / 49 (4.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	0 / 16 (0.00%)	1 / 35 (2.86%)	0 / 49 (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
Haematemesis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 35 (2.86%)	0 / 49 (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
Intussusception			
subjects affected / exposed	0 / 16 (0.00%)	1 / 35 (2.86%)	0 / 49 (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
Coeliac disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 35 (2.86%)	0 / 49 (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

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 16 (6.25%)	3 / 35 (8.57%)	3 / 49 (6.12%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas bronchitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: Placebo	Part 1: LUM/IVA	Part 2: Overall LUM/IVA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	33 / 35 (94.29%)	41 / 49 (83.67%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	3 / 35 (8.57%)	4 / 49 (8.16%)
occurrences (all)	0	3	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	2 / 35 (5.71%)	2 / 49 (4.08%)
occurrences (all)	0	2	3
Staphylococcus test positive			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	3 / 49 (6.12%)
occurrences (all)	1	1	4
Pseudomonas test positive			
subjects affected / exposed	2 / 16 (12.50%)	1 / 35 (2.86%)	1 / 49 (2.04%)
occurrences (all)	2	1	1
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	1 / 16 (6.25%)	2 / 35 (5.71%)	0 / 49 (0.00%)
occurrences (all)	2	2	0
Skin abrasion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Arthropod bite			
subjects affected / exposed	0 / 16 (0.00%)	0 / 35 (0.00%)	3 / 49 (6.12%)
occurrences (all)	0	0	3
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			

subjects affected / exposed	2 / 16 (12.50%)	3 / 35 (8.57%)	3 / 49 (6.12%)
occurrences (all)	3	5	6
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	3 / 16 (18.75%)	6 / 35 (17.14%)	2 / 49 (4.08%)
occurrences (all)	4	6	2
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 16 (0.00%)	2 / 35 (5.71%)	1 / 49 (2.04%)
occurrences (all)	0	2	1
Blepharospasm			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 16 (12.50%)	1 / 35 (2.86%)	2 / 49 (4.08%)
occurrences (all)	2	1	2
Abdominal pain			
subjects affected / exposed	2 / 16 (12.50%)	7 / 35 (20.00%)	6 / 49 (12.24%)
occurrences (all)	3	7	8
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)	4 / 35 (11.43%)	3 / 49 (6.12%)
occurrences (all)	1	4	3
Faeces pale			
subjects affected / exposed	2 / 16 (12.50%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	4 / 35 (11.43%)	2 / 49 (4.08%)
occurrences (all)	0	4	5

Abnormal faeces			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	2 / 16 (12.50%)	2 / 35 (5.71%)	4 / 49 (8.16%)
occurrences (all)	2	2	6
Frequent bowel movements			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	0 / 49 (0.00%)
occurrences (all)	1	1	0
Post-tussive vomiting			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	1 / 49 (2.04%)
occurrences (all)	1	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 16 (31.25%)	10 / 35 (28.57%)	11 / 49 (22.45%)
occurrences (all)	7	12	19
Dyspnoea			
subjects affected / exposed	2 / 16 (12.50%)	1 / 35 (2.86%)	0 / 49 (0.00%)
occurrences (all)	2	1	0
Epistaxis			
subjects affected / exposed	2 / 16 (12.50%)	2 / 35 (5.71%)	2 / 49 (4.08%)
occurrences (all)	2	2	2
Nasal polyps			
subjects affected / exposed	2 / 16 (12.50%)	1 / 35 (2.86%)	1 / 49 (2.04%)
occurrences (all)	2	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 16 (0.00%)	3 / 35 (8.57%)	0 / 49 (0.00%)
occurrences (all)	0	3	0
Nasal obstruction			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Nasal congestion			
subjects affected / exposed	4 / 16 (25.00%)	0 / 35 (0.00%)	8 / 49 (16.33%)
occurrences (all)	4	0	10
Lung infiltration			

subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	2 / 16 (12.50%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	4	0	0
Wheezing			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	2 / 49 (4.08%)
occurrences (all)	4	0	2
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 16 (0.00%)	2 / 35 (5.71%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	1 / 16 (6.25%)	3 / 35 (8.57%)	2 / 49 (4.08%)
occurrences (all)	2	3	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	1 / 49 (2.04%)
occurrences (all)	1	1	1
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 35 (5.71%)	6 / 49 (12.24%)
occurrences (all)	1	2	6
Bacterial disease carrier			
subjects affected / exposed	2 / 16 (12.50%)	0 / 35 (0.00%)	3 / 49 (6.12%)
occurrences (all)	2	0	3
Enterobiasis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	1 / 49 (2.04%)
occurrences (all)	1	0	1
Diarrhoea infectious			

subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	2 / 16 (12.50%)	3 / 35 (8.57%)	2 / 49 (4.08%)
occurrences (all)	3	3	2
Febrile infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	9 / 16 (56.25%)	15 / 35 (42.86%)	11 / 49 (22.45%)
occurrences (all)	14	25	12
Nasopharyngitis			
subjects affected / exposed	8 / 16 (50.00%)	22 / 35 (62.86%)	19 / 49 (38.78%)
occurrences (all)	16	45	31
Otitis media acute			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	1 / 16 (6.25%)	3 / 35 (8.57%)	2 / 49 (4.08%)
occurrences (all)	2	4	2
Pharyngitis streptococcal			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	0 / 49 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	2 / 35 (5.71%)	0 / 49 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	4 / 49 (8.16%)
occurrences (all)	1	2	5
Rhinitis			
subjects affected / exposed	6 / 16 (37.50%)	9 / 35 (25.71%)	8 / 49 (16.33%)
occurrences (all)	8	10	11
Tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	1 / 49 (2.04%)
occurrences (all)	1	3	1

Upper respiratory tract infection			
subjects affected / exposed	3 / 16 (18.75%)	1 / 35 (2.86%)	2 / 49 (4.08%)
occurrences (all)	5	2	2
Viral infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 35 (0.00%)	2 / 49 (4.08%)
occurrences (all)	1	0	2
Pneumonia pseudomonal			
subjects affected / exposed	1 / 16 (6.25%)	1 / 35 (2.86%)	0 / 49 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2018	Amended to include safety data analysis by IDMC and additional flexibility was added to the schedule of assessments to reduce the burden on subjects.
11 June 2018	Amended to update study phase from Phase 3b to Phase 2.
24 July 2019	Amended to allow for a delay in the Week 48 and/or Week 96 MRI assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported