



## Clinical trial results:

### A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del

#### Summary

EudraCT number	2017-004794-13
Trial protocol	Outside EU/EEA
Global end of trial date	29 October 2021

#### Results information

Result version number	v2 (current)
This version publication date	26 January 2023
First version publication date	14 May 2022
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li></ul> Addition of secondary outcomes

#### Trial information

##### Trial identification

Sponsor protocol code	VX16-809-122
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03601637
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)	EMA-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	19 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2021
Global end of trial reached?	Yes
Global end of trial date	29 October 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and pharmacokinetics (PK) of lumacaftor (LUM) and ivacaftor (IVA) in subjects 1 to less than (<) 2 years of age with cystic fibrosis (CF), homozygous for F508del (F/F).

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	07 September 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	United States: 49
Country: Number of subjects enrolled	Canada: 12
Worldwide total number of subjects	61
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)	61
Children (2-11 years)	0
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:

This study was conducted in subjects with CF aged 1 through less than 2 years of age who are homozygous for F508del.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Part A: LUM/IVA
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Arm description:

Subjects weighing 7 to less than (<)10 kilograms (kg) at screening received LUM 75 milligrams (mg)/IVA 94 mg fixed-dose combination (FDC) every 12 hours (q12h) and those weighing 10 to <14 kg at screening received LUM 100 mg/IVA 125 mg q12h for 15 days. Subjects weighing greater than or equal to (>=)14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 15 days.

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 fixed-dose combination (FDC) every 12 hours.

<b>Arm title</b>	Part B: LUM/IVA
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Arm description:

Subjects weighing 7 to <9 kg at screening received LUM 75 mg/ IVA 94 mg FDC q12h and those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg q12h for 24 weeks. Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 24 weeks. Doses were adjusted upwards for changes in weight.

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 every 12 hours.

Number of subjects in period 1[1]	Part A: LUM/IVA	Part B: LUM/IVA
	Started	14
Completed	13	43
Not completed	1	3
Adverse Event	1	1
Other	-	1
Withdrawal of Consent (not due to AE)	-	1

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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 61 subjects were enrolled in Parts A and B of the study. One subject in Part B was enrolled but not dosed in this study. Therefore, data for 60 subjects are reported in the subject disposition and baseline characteristics sections.

## Baseline characteristics

### Reporting groups

Reporting group title	Part A: LUM/IVA
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Reporting group description:

Subjects weighing 7 to less than (<)10 kilograms (kg) at screening received LUM 75 milligrams (mg)/IVA 94 mg fixed-dose combination (FDC) every 12 hours (q12h) and those weighing 10 to <14 kg at screening received LUM 100 mg/IVA 125 mg q12h for 15 days. Subjects weighing greater than or equal to (>=)14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 15 days.

Reporting group title	Part B: LUM/IVA
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Reporting group description:

Subjects weighing 7 to <9 kg at screening received LUM 75 mg/ IVA 94 mg FDC q12h and those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg q12h for 24 weeks. Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 24 weeks. Doses were adjusted upwards for changes in weight.

Reporting group values	Part A: LUM/IVA	Part B: LUM/IVA	Total
Number of subjects	14	46	60
Age categorical Units: Subjects			

Age continuous Units: months arithmetic mean standard deviation	17.2 ± 3.6	18.1 ± 3.5	-
Gender categorical Units: Subjects			
Female	7	24	31
Male	7	22	29
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	13	37	50
Unknown or Not Reported	0	7	7
Race Units: Subjects			
White	14	34	48
Black or African American	0	1	1
Asian	0	0	0
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Not collected per local regulations	0	7	7
Other	0	3	3

## End points

### End points reporting groups

Reporting group title	Part A: LUM/IVA
Reporting group description: Subjects weighing 7 to less than (<)10 kilograms (kg) at screening received LUM 75 milligrams (mg)/IVA 94 mg fixed-dose combination (FDC) every 12 hours (q12h) and those weighing 10 to <14 kg at screening received LUM 100 mg/IVA 125 mg q12h for 15 days. Subjects weighing greater than or equal to (>=)14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 15 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description: Subjects weighing 7 to <9 kg at screening received LUM 75 mg/ IVA 94 mg FDC q12h and those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg q12h for 24 weeks. Subjects weighing >=14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 24 weeks. Doses were adjusted upwards for changes in weight.	
Subject analysis set title	Part A: LUM 75 mg/IVA 94 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received LUM 75 mg/IVA 94 mg dose every 12 hours for 15 days.	
Subject analysis set title	Part A: LUM 100 mg/IVA 125 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received LUM 100 mg/IVA 125 mg dose every 12 hours for 15 days.	
Subject analysis set title	Part B: LUM 75 mg/IVA 94 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received LUM 75 mg/IVA 94 mg dose every 12 hours for 24 weeks.	
Subject analysis set title	Part B: LUM 100 mg/IVA 125 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received LUM 100 mg/IVA 125 mg dose every 12 hours for 24 weeks.	
Subject analysis set title	Part B: LUM 150 mg/IVA 188 mg
Subject analysis set type	Full analysis
Subject analysis set description: Subjects received LUM 150 mg/IVA 188 mg dose every 12 hours for 24 weeks.	

### Primary: Part A: Observed Plasma Concentrations From 3-4 hours (C3-4hr) of LUM and IVA

End point title	Part A: Observed Plasma Concentrations From 3-4 hours (C3-4hr) of LUM and IVA <sup>[1]</sup>
End point description: PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.	
End point type	Primary
End point timeframe: Day 1 and 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: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	Part A: LUM 75 mg/IVA 94 mg	Part A: LUM 100 mg/IVA 125 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1: LUM (n=7,7)	14600 (± 5560)	12600 (± 7190)		
Day 15: LUM (n=7,5)	16600 (± 9590)	13900 (± 5800)		
Day 1: IVA (n=7,7)	1620 (± 648)	1320 (± 804)		
Day 15: IVA (n=7,5)	718 (± 352)	496 (± 268)		

## Statistical analyses

No statistical analyses for this end point

### Primary: Part A: Observed Pre-dose Plasma Concentration (Ctrough) of LUM and IVA

End point title	Part A: Observed Pre-dose Plasma Concentration (Ctrough) of LUM and IVA <sup>[2]</sup>
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End point description:

PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.

End point type	Primary
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End point timeframe:

Pre-dose at Day 8 and Day 15.

Notes:

[2] - 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: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	Part A: LUM 75 mg/IVA 94 mg	Part A: LUM 100 mg/IVA 125 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 8: LUM (n=7,6)	12000 (± 8880)	12800 (± 3900)		
Day 15: LUM (n=5,6)	8380 (± 7790)	10500 (± 3070)		
Day 8: IVA (n=7,6)	169 (± 75.5)	185 (± 101)		
Day 15: IVA (n=5,6)	78.9 (± 19.1)	120 (± 60.5)		

## Statistical analyses

No statistical analyses for this end point

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**Primary: Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)**

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End point title	Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) <sup>[3][4]</sup>
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End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period. The safety and tolerability analyses were assessed for the overall treatment arm, irrespective of weight-based dose regimen. Therefore, the analysis is reported in a single Part B: LUM/IVA arm.

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End point type	Primary
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End point timeframe:

From Day 1 up to Week 26

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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: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

[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 is only applicable for Part B.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: subjects				
Subjects with TEAEs	44			
Subjects with SAEs	5			

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events**

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End point title	Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events <sup>[5]</sup>
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End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period. The safety and tolerability analyses were assessed for the overall treatment arm, irrespective of weight-based dose regimen. Therefore, the analysis is reported in a single Part A: LUM/IVA arm.

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End point type	Secondary
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End point timeframe:

From Day 1 up to Day 25

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Notes:

[5] - 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.

<b>End point values</b>	Part A: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Subjects with TEAEs	12			
Subjects with SAEs	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part A: Observed Pre-dose Plasma Concentration (Ctough) of LUM and IVA and Their Respective Metabolites (M28-LUM, M1-IVA and M6-IVA)

End point title	Part A: Observed Pre-dose Plasma Concentration (Ctough) of LUM and IVA and Their Respective Metabolites (M28-LUM, M1-IVA and M6-IVA)
End point description:	PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.
End point type	Secondary
End point timeframe:	Pre-dose at Day 8 and Day 15

<b>End point values</b>	Part A: LUM 75 mg/IVA 94 mg	Part A: LUM 100 mg/IVA 125 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
Day 8: M28-LUM (n=7,6)	1410 (± 791)	1470 (± 365)		
Day 15: M28-LUM (n=5,6)	1460 (± 1060)	1370 (± 468)		
Day 8: M1-IVA (n=7,6)	606 (± 298)	842 (± 527)		
Day 15: M1-IVA (n=5,6)	284 (± 70.2)	604 (± 394)		
Day 8: M6-IVA (n=7,6)	2380 (± 843)	3290 (± 1830)		
Day 15: M6-IVA (n=5,6)	1460 (± 763)	2800 (± 2300)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Absolute Change in Sweat Chloride

End point title	Part B: Absolute Change in Sweat Chloride <sup>[6]</sup>
End point description:	The Full Analysis Set (FAS) included all enrolled subjects who were exposed to any amount of study

drug in Part B. The pharmacodynamic analyses were assessed for the overall treatment arm, irrespective of weight-based dose regimen. Therefore, the analysis is reported in a single Part B: LUM/IVA arm.

End point type	Secondary
End point timeframe:	
From Baseline at Week 24	

Notes:

[6] - 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 secondary endpoint is only applicable for Part B.

<b>End point values</b>	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: millimole(s)/litre				
arithmetic mean (standard deviation)	-29.1 (± 13.5)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part B: Observed Pre-dose Plasma Concentration (Ctrough) of LUM and IVA and Their Respective Metabolites (M28-LUM, M1-IVA and M6-IVA)

End point title	Part B: Observed Pre-dose Plasma Concentration (Ctrough) of LUM and IVA and Their Respective Metabolites (M28-LUM, M1-IVA and M6-IVA)
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End point description:

PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively. Here 99999 represents "not applicable" categories for Ctrough.

End point type	Secondary
End point timeframe:	
Pre-dose at Day 15, Week 4, Week 12 and Week 24	

<b>End point values</b>	Part B: LUM 75 mg/IVA 94 mg	Part B: LUM 100 mg/IVA 125 mg	Part B: LUM 150 mg/IVA 188 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	44	1	
Units: nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
Day 15: LUM (n=1,43,1)	13500 (± 99999)	9030 (± 4390)	887 (± 99999)	
Week 4: LUM (n=1,43,1)	21900 (± 99999)	9370 (± 5030)	1000 (± 99999)	
Week 12: LUM (n=1,41,1)	12100 (± 99999)	9160 (± 4400)	566 (± 99999)	
Week 24: LUM (n=1,35,1)	11200 (± 99999)	8930 (± 5310)	288 (± 99999)	

Day 15: M28-LUM (n=1,43,1)	1460 (± 99999)	1260 (± 528)	786 (± 99999)
Week 4: M28-LUM (n=1,43,1)	1570 (± 99999)	1340 (± 579)	602 (± 99999)
Week 12: M28-LUM (n=1,41,1)	1740 (± 99999)	1440 (± 599)	501 (± 99999)
Week 24: M28-LUM (n=1,35,1)	1870 (± 99999)	1470 (± 548)	569 (± 99999)
Day 15: IVA (n=1,43,1)	213 (± 99999)	112 (± 68.3)	3.68 (± 99999)
Week 4: IVA (n=1,43,1)	267 (± 99999)	112 (± 82.9)	11.4 (± 99999)
Week 12: IVA (n=1,41,1)	286 (± 99999)	91.7 (± 44.7)	2.18 (± 99999)
Week 24: IVA (1,34,1)	37.1 (± 99999)	144 (± 296)	2.86 (± 99999)
Day 15: M1-IVA (n=1,43,1)	1420 (± 99999)	437 (± 291)	18.1 (± 99999)
Week 4: M1-IVA (n=1,43,1)	1930 (± 99999)	466 (± 359)	58.0 (± 99999)
Week 12: M1-IVA (n=1,41,1)	759 (± 99999)	418 (± 236)	18.3 (± 99999)
Week 24: M1-IVA (n=1,35,1)	256 (± 99999)	499 (± 613)	18.5 (± 99999)
Day 15: M6-IVA (n=1,43,1)	4740 (± 99999)	1930 (± 1460)	43.9 (± 99999)
Week 4: M6-IVA (n=1,43,1)	9090 (± 99999)	1970 (± 1490)	131 (± 99999)
Week 12: M6-IVA (n=1,41,1)	3520 (± 99999)	1950 (± 1430)	46.5 (± 99999)
Week 24: M6-IVA (n=1,35,1)	1320 (± 99999)	1740 (± 1130)	63.3 (± 99999)

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 Through Safety Follow-up Period (up to Day 25 for Part A and up to Week 26 for Part B)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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### Reporting groups

Reporting group title	Part A : LUM/IVA
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Reporting group description:

Subjects weighing 7 to <10 kg at screening received LUM 75 mg/IVA 94 mg FDC q12h and those weighing 10 to <14 kg at screening received LUM 100 mg/IVA 125 mg q12h for 15 days. Subjects  $\geq$ 14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 15 days.

Reporting group title	Part B: LUM/IVA
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Reporting group description:

Subjects weighing 7 to <9 kg at screening received LUM 75 mg/ IVA 94 mg FDC q12h and those weighing 9 to <14 kg received LUM 100 mg/IVA 125 mg FDC q12h for 24 weeks. Subjects weighing  $\geq$ 14 kg at screening received LUM 150 mg/IVA 188 mg FDC q12h for 24 weeks. Doses were adjusted upwards for changes in weight.

<b>Serious adverse events</b>	Part A : LUM/IVA	Part B: LUM/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	5 / 46 (10.87%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural fever			
subjects affected / exposed	0 / 14 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 14 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	0 / 14 (0.00%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Part A : LUM/IVA	Part B: LUM/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	42 / 46 (91.30%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	4 / 46 (8.70%)	
occurrences (all)	0	4	
Pseudomonas test positive			
subjects affected / exposed	0 / 14 (0.00%)	5 / 46 (10.87%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Lip injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	1 / 14 (7.14%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	10 / 46 (21.74%)	
occurrences (all)	1	15	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	5 / 46 (10.87%)	
occurrences (all)	1	7	
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	3 / 46 (6.52%) 3	
Vomiting subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	8 / 46 (17.39%) 9	
Flatulence subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 46 (2.17%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 4	16 / 46 (34.78%) 27	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	4 / 46 (8.70%) 6	
Rhinorrhoea subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 5	5 / 46 (10.87%) 9	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 4	4 / 46 (8.70%) 4	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 46 (2.17%) 1	
Infections and infestations Ear infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	5 / 46 (10.87%) 5	
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	8 / 46 (17.39%) 12	
Influenza subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	0 / 46 (0.00%) 0	

Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	4 / 46 (8.70%) 4	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	6 / 46 (13.04%) 9	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	5 / 46 (10.87%) 6	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 46 (2.17%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2019	Amended to update the planned dosing regimen to add lower dose of LUM/IVA in Parts A and B and, to adjust the weight bound of LUM/IVA in Part B.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported