Clinical trial results:
A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Lumacaftor in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2017-001078-41
Trial protocol	Outside EU/EEA
Global end of trial date	28 October 2015

Results information

Result version number	v1 (current)
This version publication date	19 June 2017
First version publication date	19 June 2017

Trial information

Trial identification

Sponsor protocol code	VX13-809-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01897233
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001582-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To evaluate the pharmacokinetics (PK) of multiple doses of lumacaftor (LUM, VX-809) in combination with ivacaftor (IVA, VX-770); Part B: To evaluate the safety and tolerability of LUM in combination with IVA through Week 24.

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	12 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	62
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	62
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 2 parts – Part A and Part B. Part A consisted of 2 cohorts, in which subjects aged 6 to 8 years were enrolled in Cohort 1 and subjects aged 9 to 11 years were enrolled in Cohort 2. Part B consisted of a single cohort. Subjects from Part A may have also participated in Part B of the study.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A Cohort 1: LUM/IVA

Arm description:

Subjects aged 6 through 8 years received LUM 200 milligram (mg) in fixed-dose combination with IVA 250 mg orally every 12 hours (q12h) for 14 days.

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

Dosage and administration details:

LUM 200 mg in combination with IVA 250 mg as fixed-dose combination tablet orally q12h for 14 days.

Arm title	Part A Cohort 2: LUM/IVA

Arm description:

Subjects aged 9 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 14 days.

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

Dosage and administration details:

LUM 200 mg in combination with IVA 250 mg as fixed-dose combination tablet orally q12h for 14 days.

Arm title	Part B: LUM/IVA

Arm description:

Subjects aged 6 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Lumacaftor Plus Ivacaftor Combination
Investigational medicinal product code	VX-809+VX-770
Other name	LUM+IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LUM 200 mg in combination with IVA 250 mg as fixed-dose combination tablet orally q12h for 24 weeks.

Number of subjects in period 1	Part A Cohort 1: LUM/IVA	Part A Cohort 2: LUM/IVA	Part B: LUM/IVA
Started	5	5	58
Completed	5	5	54
Not completed	0	0	4
Consent withdrawn by subject	-	-	2
Physician decision	-	-	1
Adverse Event	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A Cohort 1: LUM/IVA
Reporting group description:	
Subjects aged 6 through 8 years received LUM 200 milligram (mg) in fixed-dose combination with IVA 250 mg orally every 12 hours (q12h) for 14 days.	
Reporting group title	Part A Cohort 2: LUM/IVA
Reporting group description:	
Subjects aged 9 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 14 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description:	
Subjects aged 6 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 24 weeks.	

Reporting group values	Part A Cohort 1: LUM/IVA	Part A Cohort 2: LUM/IVA	Part B: LUM/IVA
Number of subjects	5	5	58
Age categorical			
Units: Subjects			

Age continuous			
Data was planned to be reported separately for Part A and Part B of the study.			
Units: years			
arithmetic mean	6.6	9.6	9.1
standard deviation	± 0.89	± 0.89	± 1.53
Gender categorical			
Data was planned to be reported separately for Part A and Part B of the study.			
Units: Subjects			
Female	1	1	31
Male	4	4	27

Reporting group values	Total		
Number of subjects	68		
Age categorical			
Units: Subjects			

Age continuous			
Data was planned to be reported separately for Part A and Part B of the study.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Data was planned to be reported separately for Part A and Part B of the study.			
Units: Subjects			
Female	33		
Male	35		

End points

End points reporting groups

Reporting group title	Part A Cohort 1: LUM/IVA
Reporting group description:	
Subjects aged 6 through 8 years received LUM 200 milligram (mg) in fixed-dose combination with IVA 250 mg orally every 12 hours (q12h) for 14 days.	
Reporting group title	Part A Cohort 2: LUM/IVA
Reporting group description:	
Subjects aged 9 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 14 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description:	
Subjects aged 6 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 24 weeks.	
Subject analysis set title	Part A Overall Arm: LUM/IVA
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects aged 6 through 11 years who received LUM 200 mg in fixed--dose combination with IVA 250 mg orally q12h for 14 days.	

Primary: Part A: Observed Plasma Concentration of Lumacaftor (LUM) and Ivacaftor (IVA) at Hour 4 Post-dose (C4h) on Day 1

End point title	Part A: Observed Plasma Concentration of Lumacaftor (LUM) and Ivacaftor (IVA) at Hour 4 Post-dose (C4h) on Day 1[1]
End point description:	
The Pharmacokinetic (PK) Set included all enrolled subjects who received the study drug and for whom the primary PK data were considered to be sufficient and interpretable.	
End point type	Primary
End point timeframe:	
4 hours post-morning dose on Day 1	

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 reported, inferential statistics were not planned for this primary endpoint.

End point values	Part A Overall Arm: LUM/IVA			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
LUM	15200 (± 6740)			
IVA	1920 (± 727)			

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Observed Plasma Concentration of Lumacaftor (LUM) and Ivacaftor (IVA) at Hour 4 Post-dose (C4h) on Day 14

End point title	Part A: Observed Plasma Concentration of Lumacaftor (LUM) and Ivacaftor (IVA) at Hour 4 Post-dose (C4h) on Day 14[2]

End point description:

The PK Set included all enrolled subjects who received the study drug and for whom the primary PK data were considered to be sufficient and interpretable.

End point type	Primary

End point timeframe:

4 hours post-morning dose on Day 14

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 reported, inferential statistics were not planned for this primary endpoint.

End point values	Part A Overall Arm: LUM/IVA			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: ng/mL				
arithmetic mean (standard deviation)				
LUM	24500 (± 10400)			
IVA	622 (± 322)			

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Area Under the Plasma Concentration-Time Curve From Time 0 to End of Dosing Interval (AUCtau) of Lumacaftor (LUM) and Ivacaftor (IVA)

End point title	Part A: Area Under the Plasma Concentration-Time Curve From Time 0 to End of Dosing Interval (AUCtau) of Lumacaftor (LUM) and Ivacaftor (IVA)[3]

End point description:

The AUCtau is the area under the concentration versus time curve from time 0 to time tau, where tau is the time at the end of dosing interval. The PK Set included all enrolled subjects who received the study drug and for whom the primary PK data were considered to be sufficient and interpretable.

End point type	Primary

End point timeframe:

Day 14 (pre-morning dose, 4, 6, 12, and 24 hours post-morning dose for LUM; pre-morning dose, 2, 4, 6, 12 hours post-morning dose for IVA)

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 reported, inferential statistics were not planned for this primary endpoint.

End point values	Part A Overall Arm: LUM/IVA			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: ng*hr/mL				
median (full range (min-max))				
LUM	387600 (280700 to 640800)			
IVA	6838 (2689 to 12100)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[4][5]

End point description:

AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed. AE includes serious as well as non-serious AEs. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, inpatient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. AEs with start date or increased severity on or after the first study drug dose to Week 26 were considered treatment-emergent. The Safety Set included all subjects who received any amount of Part B study drug.

End point type	Primary

End point timeframe:

Day 1 up to Week 26

Notes:

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

[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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Subjects				
AEs	55			
SAEs	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Observed Plasma Concentration of Lumacaftor Metabolite (M28-LUM) and Ivacaftor Metabolites (M1-IVA and M6-IVA) at Hour 4 Post-dose (C4h) on Day 1 and 14

End point title	Part A: Observed Plasma Concentration of Lumacaftor Metabolite (M28-LUM) and Ivacaftor Metabolites (M1-IVA and M6-IVA) at Hour 4 Post-dose (C4h) on Day 1 and 14

End point description:

The PK Set included all enrolled subjects who received the study drug and for whom the primary PK data were considered to be sufficient and interpretable.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2, 4, 6 and 12 hours post-morning dose); Day 14 (pre-dose, 4, 6, 12, and anytime between 24 to 96 hours post-morning dose)

End point values	Part A Overall Arm: LUM/IVA			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: ng/mL				
arithmetic mean (standard deviation)				
M28-LUM (Day 1)	176 (± 79)			
M1-IVA (Day 1)	3940 (± 1380)			
M6-IVA (Day 1)	1810 (± 981)			
M28-LUM (Day 14)	2040 (± 1230)			
M1-IVA (Day 14)	2380 (± 1360)			
M6-IVA (Day 14)	4240 (± 1990)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Part A: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)[6]

End point description:

AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed. AE includes serious as well as non-serious AEs. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, inpatient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event.AEs with start date or increased severity on or after the first study drug dose through the end of Part A were considered treatment-emergent. Safety Set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 up to Day 28

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: Only arms which are applicable to the endpoint are reported.

End point values	Part A Cohort 1: LUM/IVA	Part A Cohort 2: LUM/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Subjects				
AEs	4	3		
SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B: Average Absolute Change From Baseline in Sweat Chloride at Day 15 and at Week 4[7]

End point description:

Sweat samples were collected using an approved collection device. Baseline was defined as the average of the measurements at screening and on Day 1 pre-dose. Average of Day 15 and Week 4 measurements was taken and change was calculated as: Average (Day 15 and Week 4 measurement) minus Baseline measurement. The Full Analysis Set (FAS) included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 15 and Week 4

Notes:

[7] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-19.7 (-23.2 to -16.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Sweat Chloride From Week 24 at Week 26

End point title	Part B: Absolute Change in Sweat Chloride From Week 24 at Week 26[8]

End point description:

Sweat samples were collected using an approved collection device. Change = Week 26 minus Week 24. The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 24, Week 26

Notes:

[8] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: mmol/L				
least squares mean (confidence interval 95%)	21.3 (18.6 to 24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in Body Mass Index (BMI) at Week 24

End point title	Part B: Absolute Change From Baseline in Body Mass Index (BMI) at Week 24[9]

End point description:

BMI was defined as weight in kilogram (kg) divided by height*height in square meter (m^2). The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[9] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Kilogram per square meter (kg/m^2)				
least squares mean (confidence interval 95%)	0.64 (0.46 to 0.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in BMI-for-age Z-score at Week 24

End point title	Part B: Absolute Change From Baseline in BMI-for-age Z-score at Week 24[10]

End point description:

BMI was defined as weight in kg divided by height*height in m^2. z-score is a statistical measure to evaluate how a single data point compares to a standard. It describes whether a mean was above or below the standard and how unusual the measurement is, with range from -infinity to +infinity; where 0: same mean, greater than (>) 0: a greater mean, and lesser than (<) 0: a lesser mean than the standard. BMI, adjusted for age and sex, was analyzed as BMI-for-age z-score (BMI z-score). The BMI-for-age z-scores were calculated using National Center for Health Statistics growth charts. The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[10] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Z-score				
least squares mean (confidence interval 95%)	0.15 (0.08 to 0.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in Weight at Week 24

End point title	Part B: Absolute Change From Baseline in Weight at Week

End point description:

The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[11] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Kilograms (kg)				
least squares mean (confidence interval 95%)	2.6 (2.2 to 3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in Weight-for-age Z-score at Week 24

End point title	Part B: Absolute Change From Baseline in Weight-for-age Z-score at Week 24[12]

End point description:

Z-score is a statistical measure to evaluate how a single data point compares to a standard. It describes whether a mean was above or below the standard and how unusual the measurement is, with range from -infinity to +infinity; where 0: same mean, >0: a greater mean, and <0: a lesser mean than the standard. Weight, adjusted for age and sex, was analyzed as weight-for-age z-score (weight z-score). The weight-for-age z-scores were calculated using National Center for Health Statistics growth charts. The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[12] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Z-score				
least squares mean (confidence interval 95%)	0.13 (0.07 to 0.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in Height at Week 24

End point title	Part B: Absolute Change From Baseline in Height at Week 24[13]

End point description:

The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[13] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Centimeter (cm)				
least squares mean (confidence interval 95%)	2.9 (2.6 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in Height-for-age Z-score at Week 24

End point title	Part B: Absolute Change From Baseline in Height-for-age Z-score at Week 24[14]

End point description:

Z-score is a statistical measure to evaluate how a single data point compares to a standard. It describes whether a mean was above or below the standard and how unusual the measurement is, with range from -infinity to +infinity; where 0: same mean, >0: a greater mean, and <0: a lesser mean than the standard. Height, adjusted for age and sex, was analyzed as height-for-age z-score (height z-score). The height-for-age z-scores were calculated using National Center for Health Statistics growth charts. The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[14] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Z-score				
least squares mean (confidence interval 95%)	0.03 (-0.02 to 0.09)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score at Week 24[15]

End point description:

The CFQ-R is a validated patient-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms (for example, coughing, congestion, wheezing), score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[15] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Units on a scale				
least squares mean (confidence interval 95%)	5.4 (1.4 to 9.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Domains at Week 24

End point title	Part B: Absolute Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Domains at Week 24[16]

End point description:

The TSQM is a 14-item self-administered questionnaire which measures subject's experiences with their medication on four dimensions: effectiveness, side effects, convenience and global satisfaction. For each dimension, responses are added and transformed to a scale from 0 to 100, where higher scores indicate greater satisfaction. The FAS included all Part B enrolled subjects who were exposed to any amount of Part B study drug. Here "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

Notes:

[16] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Change at Week 24: Effectiveness	9.2 (4.3 to 14.1)			
Change at Week 24: Side Effects	-0.3 (-1.4 to 0.8)			
Change at Week 24: Convenience	11.1 (7.1 to 15.1)			
Change at Week 24: Global Score	3.6 (-2 to 9.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Pre-dose Concentration (Ctrough) and 3 to 6 Hours Post-dose Concentration (C3-6hr) of Lumacaftor, Lumacaftor Metabolite (M28-LUM), Ivacaftor and Ivacaftor Metabolites (M1-IVA and M6-IVA)

End point title	Part B: Pre-dose Concentration (Ctrough) and 3 to 6 Hours Post-dose Concentration (C3-6hr) of Lumacaftor, Lumacaftor Metabolite (M28-LUM), Ivacaftor and Ivacaftor Metabolites (M1-IVA and M6-IVA)[17]

End point description:

Ctrough and C3-6hr for lumacaftor, M28 lumacaftor (lumacaftor metabolite), ivacaftor, M1 ivacaftor (ivacaftor metabolite), and M6 ivacaftor (ivacaftor metabolite) were calculated. Ctrough was observed pre-dose concentration. C3-6hr was observed concentration at 3 to 6 hours post- dose. The PK Set included all enrolled subjects who received the study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "n" signifies those subjects who were evaluable at the specified time point for the given category.

End point type	Secondary

End point timeframe:

For Ctrough: pre-morning dose on Week 4, Week 6 and Week 24; For C3-6hr: 3 to 6 hours post-morning dose on Day 1, 15 and Week 4

Notes:

[17] - 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: Only arm which is applicable to the endpoint is reported.

End point values	Part B: LUM/IVA			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: ng/mL				
arithmetic mean (standard deviation)				
C3-6h LUM (Day 1) (n=57)	17100 (± 6260)			
C3-6h IVA (Day 1) (n=57)	1980 (± 850)			
C3-6h M28-LUM (Day 1) (n=57)	186 (± 96.3)			
C3-6h M1-IVA (Day 1) (n=57)	4170 (± 1940)			
C3-6h M6-IVA (Day 1) (n=57)	2040 (± 1650)			

C3-6h LUM (Day 15) (n=55)	21400 (± 6850)			
C3-6h IVA (Day 15) (n=55)	751 (± 433)			
C3-6h M28-LUM (Day 15) (n=55)	1660 (± 843)			
C3-6h M1-IVA (Day 15) (n=55)	2670 (± 1330)			
C3-6h M6-IVA (Day 15) (n=55)	4360 (± 2340)			
C3-6h LUM (Week 4) (n=54)	22000 (± 8470)			
C3-6h IVA (Week 4) (n=54)	779 (± 389)			
C3-6h M28-LUM (Week 4) (n=54)	1730 (± 884)			
C3-6h M1-IVA (Week 4) (n=54)	2800 (± 1410)			
C3-6h M6-IVA (Week 4) (n=54)	4690 (± 3360)			
Ctrough LUM (Week 4) (n=53)	12300 (± 6780)			
Ctrough IVA (Week 4) (n=53)	171 (± 228)			
Ctrough M28-LUM (Week 4) (n=53)	1780 (± 903)			
Ctrough M1-IVA (Week 4) (n=53)	684 (± 816)			
Ctrough M6-IVA (Week 4) (n=53)	2490 (± 2150)			
Ctrough LUM (Week 16) (n=53)	11500 (± 6020)			
Ctrough IVA (Week 16) (n=52)	153 (± 150)			
Ctrough M28-LUM (Week 16) (n=53)	1610 (± 859)			
Ctrough M1-IVA (Week 16) (n=53)	690 (± 627)			
Ctrough M6-IVA (Week 16) (n=53)	2360 (± 1570)			
Ctrough LUM (Week 24) (n=51)	11400 (± 5300)			
Ctrough IVA (Week 24) (n=51)	118 (± 87.2)			
Ctrough M28-LUM (Week 24) (n=51)	1710 (± 947)			
Ctrough M1-IVA (Week 24) (n=51)	493 (± 409)			
Ctrough M6-IVA (Week 24) (n=51)	1790 (± 1180)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Part A: Day 1 up to Day 28; Part B: Day 1 up to Week 26	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Part A Cohort 1: LUM/IVA
Reporting group description: Subjects aged 6 through 8 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 14 days.	
Reporting group title	Part A Cohort 2: LUM/IVA
Reporting group description: Subjects aged 9 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 14 days.	
Reporting group title	Part B: LUM/IVA
Reporting group description: Subjects aged 6 through 11 years received LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 24 weeks.	

Serious adverse events	Part A Cohort 1: LUM/IVA	Part A Cohort 2: LUM/IVA	Part B: LUM/IVA
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	4 / 58 (6.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part A Cohort 1: LUM/IVA	Part A Cohort 2: LUM/IVA	Part B: LUM/IVA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	3 / 5 (60.00%)	55 / 58 (94.83%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	6 / 58 (10.34%)
occurrences (all)	1	0	6
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	6
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Application site erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Application site urticaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Application site vesicles			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Vessel puncture site reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
House dust allergy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Mycotic allergy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	29 / 58 (50.00%)
occurrences (all)	1	5	44
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	12 / 58 (20.69%)
occurrences (all)	0	1	16
Sputum increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	8 / 58 (13.79%)
occurrences (all)	0	0	11
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Lower respiratory tract congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Rhinorrhoea			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	5 / 58 (8.62%)
occurrences (all)	0	0	5
Increased viscosity of upper respiratory secretion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Pharyngeal erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Rales			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Respiration abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	3
Sneezing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2

Nasal polyps			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Rhonchi			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	8
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	4
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1

Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Mean cell haemoglobin concentration decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Pseudomonas test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Pulmonary function test decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Blood bicarbonate decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Blood creatinine decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Blood urea increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Crystal urine present			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Eosinophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Streptococcus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Weight decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Forced expiratory volume decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Arthropod bite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Foot fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Ligament sprain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Upper limb fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	12 / 58 (20.69%)
occurrences (all)	2	1	16
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Sinus headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	3
Lethargy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Cataract			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	8 / 58 (13.79%)
occurrences (all)	1	0	9
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	5 / 58 (8.62%)
occurrences (all)	1	0	6
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	4 / 58 (6.90%)
occurrences (all)	1	0	5
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	4
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	7
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	6
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	6 / 58 (10.34%)
occurrences (all)	0	0	8
Faeces soft			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Frequent bowel movements			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Faecal volume increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	4
Dermatitis contact			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Dandruff			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Urticaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Myalgia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	11 / 58 (18.97%)
occurrences (all)	0	0	13
Gastroenteritis viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Pharyngitis streptococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	4
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Abscess limb			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Gastroenteritis bacterial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Impetigo			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Otitis externa			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Staphylococcal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Tinea infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	3 / 58 (5.17%)
occurrences (all)	0	0	3
Increased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2013	Added Part B (a 24 week, open label Treatment Period).
30 September 2014	Added evaluation of sweat chloride and liver function to Part B.
12 March 2015	Added the PK evaluation of M28-LUM and M6-IVA to the secondary objectives and endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to limited sampling and instances of missing data, C4h was reported instead of Cmax as an approximation of maximum concentration. Sparse PK sampling scheme was optimized around parent compounds which limited the estimation of AUC for metabolites.

Notes: