



Clinical trial results:

A Phase 3, Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation

Summary

EudraCT number	2012-003989-40
Trial protocol	SE IT CZ DE IE GB NL
Global end of trial date	29 April 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	VX12-809-103
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01807923
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, MA, United States, 02210-1862
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	29 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lumacaftor in combination with ivacaftor at Week 24 in subjects aged 12 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene.

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	28 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	United States: 261
Worldwide total number of subjects	549
EEA total number of subjects	211

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)	0
Adolescents (12-17 years)	158
Adults (18-64 years)	391
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 187, 185, and 187 subjects were randomized in 'Placebo', 'LUM 600 mg qd/IVA 250 mg q12h', and 'LUM 400 mg q12h/IVA 250 mg q12h', respectively; of which 184, 183, and 182 subjects in respective groups received at least 1 dose of the study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to lumacaftor (LUM, VX-809) and ivacaftor (IVA, VX-770) tablet every 12 hours (q12h), up to Week 24.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to LUM and IVA tablet q12h, up to Week 24.

Arm title	LUM 600 mg qd/IVA 250 mg q12h
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Arm description:

LUM 600 milligram (mg) plus IVA 250 mg supplied as fixed-dose combination (FDC) tablets in the morning and IVA 250 mg film-coated tablet in the evening, up to Week 24.

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 600 mg plus IVA 250 mg supplied as FDC tablet in the morning up to week 24.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor 250 mg film-coated tablet in the evening up to Week 24.

Arm title	LUM 400 mg q12h/IVA 250 mg q12h
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Arm description:

LUM 400 mg plus IVA 250 mg supplied as FDC tablets in the morning and in the evening, up to Week 24.

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 400 mg plus IVA 250 mg supplied as FDC tablet in the morning and in the evening, up to Week 24.

Number of subjects in period 1	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h
Started	184	183	182
Completed	182	179	176
Not completed	2	4	6
Physician decision	-	-	1
Adverse Event	2	1	2
Not Eligible (Genotype)	-	-	1
Withdrawal of Consent (not due to AE)	-	3	2

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to lumacaftor (LUM, VX-809) and ivacaftor (IVA, VX-770) tablet every 12 hours (q12h), up to Week 24.	
Reporting group title	LUM 600 mg qd/IVA 250 mg q12h
Reporting group description: LUM 600 milligram (mg) plus IVA 250 mg supplied as fixed-dose combination (FDC) tablets in the morning and IVA 250 mg film-coated tablet in the evening, up to Week 24.	
Reporting group title	LUM 400 mg q12h/IVA 250 mg q12h
Reporting group description: LUM 400 mg plus IVA 250 mg supplied as FDC tablets in the morning and in the evening, up to Week 24.	

Reporting group values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h
Number of subjects	184	183	182
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	25 ± 10.8	24.7 ± 9.71	25.5 ± 10.09
Gender categorical Units: Subjects			
Female	84	86	84
Male	100	97	98

Reporting group values	Total		
Number of subjects	549		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	254		
Male	295		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to lumacaftor (LUM, VX-809) and ivacaftor (IVA, VX-770) tablet every 12 hours (q12h), up to Week 24.	
Reporting group title	LUM 600 mg qd/IVA 250 mg q12h
Reporting group description: LUM 600 milligram (mg) plus IVA 250 mg supplied as fixed-dose combination (FDC) tablets in the morning and IVA 250 mg film-coated tablet in the evening, up to Week 24.	
Reporting group title	LUM 400 mg q12h/IVA 250 mg q12h
Reporting group description: LUM 400 mg plus IVA 250 mg supplied as FDC tablets in the morning and in the evening, up to Week 24.	

Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 24

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 24
End point description: Absolute change from baseline at Week 24 was assessed as the average treatment effect at Week 16 and at Week 24. FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Hankinson and Wang standards were used to calculate percent predicted FEV1 (for age, gender, race and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 12 to 17 years and for female subjects aged 12 to 15 years. Analysis was performed on Full Analysis Set (FAS) included all randomized subjects who received any amount of study drug. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline, Week 16 and 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	176	172	
Units: percent predicted of FEV1				
least squares mean (standard error)	-0.44 (± 0.524)	3.59 (± 0.525)	2.16 (± 0.53)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Analysis was performed using mixed-effects model for repeated measures (MMRM) model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male	

versus female), age group at baseline (less than (<)18 versus greater than equal to (>=) 18 years old), and percent predicted FEV1 severity at Screening (<70 versus >=70).

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	4.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.62
upper limit	5.44

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis was performed using MMRM model, as described in Statistical Analysis 1.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	4.01

Secondary: Relative Change From Baseline in Percent Predicted FEV1 at Week 24

End point title	Relative Change From Baseline in Percent Predicted FEV1 at Week 24
End point description:	
Relative change from baseline at week 24 was assessed as the average treatment effect at Week 16 and at Week 24. FEV1 and percent predicted FEV1 are defined in primary endpoint. Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 16 and 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	176	172	
Units: percent change				
least squares mean (standard error)	-0.34 ($\pm$ 0.913)	6.39 ($\pm$ 0.914)	3.99 ($\pm$ 0.923)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus $\geq$ 18 years old), and percent predicted FEV1 severity at Screening (<70 versus $\geq$ 70).	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	6.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.27
upper limit	9.19

Statistical analysis title	Statistical Analysis 2
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0006
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	4.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.86
upper limit	6.8

Notes:

[1] - Analysis was performed using MMRM model, as described in Statistical Analysis 1.

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

End point title	Absolute Change From Baseline in Body Mass Index (BMI) at Week 24
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End point description:

BMI was defined as weight in kilogram (kg) divided by height*height in square meter (m²). Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	178	176	
Units: kilogram per square meter (kg/m ²)				
least squares mean (standard error)	0.19 (± 0.07)	0.35 (± 0.07)	0.32 (± 0.071)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline BMI.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1122
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.35

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Analysis was performed using MMRM model, as described in Statistical Analysis 1.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
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Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1938
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.32

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

End point title	Absolute Change From Baseline in (Cystic Fibrosis Questionnaire-Revised) CFQ R Respiratory Domain Score at Week 24
End point description: The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms (for example, coughing, congestion, wheezing), the scaled score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	176	172	
Units: units on a scale				
least squares mean (standard error)	1.1 (± 1.161)	4.98 (± 1.178)	2.6 (± 1.192)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline CFQ-R respiratory domain score.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0168 ^[2]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	3.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	7.05

Notes:

[2] - This test is considered nominally significant because a hierarchical procedure was used and was broken prior to this test.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis was performed using MMRM model, as described in Statistical Analysis 1.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3569
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	4.69

Secondary: Percentage of subjects With Response Based on Percent Predicted FEV1

End point title	Percentage of subjects With Response Based on Percent Predicted FEV1
End point description:	
A subject was considered as a responder if the subject had $\geq 5\%$ increase from baseline in average percent predicted FEV1 at Week 16 and at Week 24 (relative change). FEV1 and percent predicted FEV1 are defined in primary endpoint. Analysis was performed on FAS. A subject with a missing average relative change from baseline in percent predicted FEV1 at Week 16 and at Week 24 was considered as a non-responder.	
End point type	Secondary
End point timeframe:	
Week 16 and 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	183	182	
Units: percentage of subjects				
number (not applicable)	22.3	46.4	36.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Odds Ratio (OR) and 95% confidence intervals (Cis) are Mantel-Haenszel estimates. P values are from a Cochran-Mantel-Haenszel test stratified by sex (male versus female), age group at baseline (<18 versus ≥18 years old), and percent predicted FEV1 severity at Screening (<70 versus ≥70).

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.9378
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8786
upper limit	4.5941

Notes:

[3] - This test is considered nominally significant because a hierarchical procedure was used and was broken prior to this test.

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

Comparison groups	Placebo v LUM 400 mg q12h/IVA 250 mg q12h
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 ^[4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.0592
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.292
upper limit	3.2819

Notes:

[4] - This test is considered nominally significant because a hierarchical procedure was used and was broken prior to this test.

Secondary: Number of Pulmonary Exacerbation Events

End point title	Number of Pulmonary Exacerbation Events
End point description: The total number of days on study is equal to the Week 24 date or the last dose date (whichever occurred last) minus the first dose date plus 1. The total number of years (48 weeks) on study is equal to the number of days on study divided by 336. Pulmonary exacerbation events per year (48 weeks) are reported. Analysis was performed on FAS.	
End point type	Secondary
End point timeframe: through Week 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	183	182	
Units: pulmonary exacerbation events per year				
number (not applicable)	1.07	0.77	0.71	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Analysis was performed using regression analysis for a negative binomial distribution with sex (male versus female), age group at baseline (<18 versus ≥18 years old), and percent predicted FEV1 severity at Screening (<70 versus ≥70) as covariates with the logarithm of time on study as the offset.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0491
Method	Negative Binomial Regression
Parameter estimate	Event Rate Ratio
Point estimate	0.7186
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.517
upper limit	0.9987

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0169 ^[5]
Method	Negative Binomial Regression
Parameter estimate	Event Rate Ratio
Point estimate	0.6643
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4749
upper limit	0.9291

Notes:

[5] - This test is considered nominally significant because a hierarchical procedure was used and was broken prior to this test.

Secondary: Absolute Change From Baseline in Weight at Week 24

End point title	Absolute Change From Baseline in Weight at Week 24
End point description:	
Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	178	176	
Units: kilograms (kg)				
least squares mean (standard error)	0.93 (± 0.202)	1.34 (± 0.205)	1.23 (± 0.205)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline weight.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo

Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1565
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.96

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Analysis was performed as described in Statistical Analysis 1.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2992
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.86

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

End point title	Absolute Change From Baseline in BMI-for-age Z-score at Week 24
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; 0: same mean, >0: a greater mean, and <0: a lesser mean than the standard. BMI-for-age z-score was calculated by using Centers for Disease Control and Prevention (CDC) growth charts for the pediatric population. Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint. Only subjects who were <20 years of age were analyzed.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	65	58	
Units: z-score				
least squares mean (standard error)	0.0153 ($\pm$ 0.04886)	0.1132 ($\pm$ 0.05081)	0.0933 ($\pm$ 0.05431)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus $\geq$ 18 years old), percent predicted FEV1 severity at Screening (<70 versus $\geq$ 70), and baseline BMI z-score.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1539
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.233

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis was performed as described in Statistical Analysis 1.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2713
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.0781
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0615
upper limit	0.2176

Secondary: Time-to-First Pulmonary Exacerbation

End point title	Time-to-First Pulmonary Exacerbation
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End point description:

Time to first pulmonary exacerbation was assessed using Cox Regression. For subjects who completed 24 weeks of treatment, subjects without a pulmonary exacerbation before treatment completion were considered censored at the time of treatment completion or at the Week 24 Visit (whichever occurred last). For subjects who prematurely discontinued study treatment, subjects without a pulmonary exacerbation through the Week 24 Visit were considered censored at the time of the Week 24 Visit. Analysis was performed on FAS. The number 99999 represents data not available because median time was not reached as less than 50% of subjects had the event of interest.

End point type	Secondary
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End point timeframe:

through Week 24

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	183	182	
Units: days				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Analysis was performed using Cox proportional hazard regression, time is the time-to-first event or censoring, with adjustment for sex (male versus female), age group at baseline (<18 versus ≥18 years old), and percent predicted FEV1 severity at Screening (<70 versus ≥70).

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
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Number of subjects included in analysis	367
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.0396
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Method	Cox Proportional Hazard Regression
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Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
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Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0385
Method	Cox Proportional Hazard Regression

Secondary: Percentage of subjects With At Least 1 Pulmonary Exacerbation Event

End point title	Percentage of subjects With At Least 1 Pulmonary Exacerbation Event
End point description:	
Analysis was performed on FAS.	
End point type	Secondary
End point timeframe:	
through Week 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	183	182	
Units: percentage of subjects				
number (not applicable)	39.7	30.1	30.2	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
OR and 95% confidence intervals (CIs) are Mantel-Haenszel estimates. P values are from a Cochran-Mantel-Haenszel test stratified by sex (male versus female), age group at baseline (<18 versus ≥18 years old), and percent predicted FEV1 severity at Screening (<70 versus ≥70).	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0552
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.6565
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4266
upper limit	1.0103

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Analysis was performed as described in Statistical Analysis 1.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0512
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.6438
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4142
upper limit	1.0005

Secondary: Absolute Change From Baseline in Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score at Week 24

End point title	Absolute Change From Baseline in Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score at Week 24
End point description: EQ-5D-3L: subject rated questionnaire to assess health-related quality of life. It consists of EQ-5D descriptive system and EQ-5D Visual Analog Scale (VAS). EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems (1), some problems (2), and extreme problems (3). The 5 dimensional 3-level systems are converted into a single index utility score. Values for theoretically possible health states are calculated using a regression model and weighted according to the social preferences of the Unites States (US) general population. For this population, the possible EQ-5D-3L index scores ranges from -0.11 (that is, 3 for all 5 dimensions) to 1.0 (that is, 1 for all 5 dimensions), where higher scores indicate a better health state. Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	179	175	170	
Units: units on a scale				
least squares mean (standard error)	0.0006 (± 0.00739)	0.0066 (± 0.00746)	0.01 (± 0.00757)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline EQ5D3L index score.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5604
Method	MMRM
Parameter estimate	LS Mean Difference]
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0142
upper limit	0.0262

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Analysis was performed as described in Statistical Analysis 1.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3613
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.0095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0109
upper limit	0.0298

Secondary: Absolute Change From Baseline in EQ-5D-3L VAS Score at Week 24

End point title	Absolute Change From Baseline in EQ-5D-3L VAS Score at
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End point description:

The EQ-5D-3L VAS records the subjects self-rated health on a vertical, visual analogue scale where the best state a subject can imagine is marked 100 and the worst state a subject can imagine is marked 0, higher scores indicates a better health state. Analysis was performed on FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type

Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	180	173	171	
Units: units on a scale				
least squares mean (standard error)	1.4 ($\pm$ 1.03)	3.5 ($\pm$ 1.04)	2.8 ($\pm$ 1.04)	

Statistical analyses

Statistical analysis title

Statistical Analysis 1

Statistical analysis description:

Analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus $\geq$ 18 years old), percent predicted FEV1 severity at Screening (<70 versus $\geq$ 70), and baseline EQ-5D-3L VAS score.

Comparison groups	Placebo v LUM 600 mg qd/IVA 250 mg q12h
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1342
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	4.9

Statistical analysis title

Statistical Analysis 2

Statistical analysis description:

Analysis was performed as described in Statistical Analysis 1.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
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Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3071
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	4.2

Secondary: Absolute Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Domain Scores at Week 24

End point title	Absolute Change From Baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) Domain Scores at Week 24
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End point description:

The TSQM is a 14-item self-administered questionnaire which measures subjects 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. Analysis was performed on FAS. Here, "n" signifies subjects who were evaluable for specified category for each arm, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	183	182	
Units: units on a scale				
least squares mean (standard error)				
Effectiveness (n = 163, 156, 144)	-5.3 (± 1.643)	0.19 (± 1.666)	0.5 (± 1.726)	
Side Effects (n = 162, 154, 143)	2.23 (± 1.119)	-1.94 (± 1.141)	-2.51 (± 1.179)	
Convenience (n = 163, 154, 144)	4.37 (± 1.504)	4.98 (± 1.54)	7.45 (± 1.579)	
Global Satisfaction (n= 163, 154, 144)	-10.49 (± 1.863)	-5 (± 1.906)	-3.77 (± 1.956)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Effectiveness: analysis was performed using MMRM model including treatment, visit, and treatment-by-

visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline TSQM effectiveness score. Actual number of subjects included in analysis were 319.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	9.96

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Effectiveness: analysis was performed as described in Statistical Analysis 1. Actual number of subjects included in analysis were 307.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0126
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	10.35

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Side Effects: analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline TSQM side effects score. Actual number of subjects included in analysis were 316.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.23
upper limit	-1.13

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

Side Effects: analysis was performed as described in Statistical Analysis 1. Actual number of subjects included in analysis were 305.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-4.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.85
upper limit	-1.63

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

Convenience: analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline TSQM convenience score. Actual number of subjects included in analysis were 317.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7721
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	4.71

Statistical analysis title	Statistical Analysis 6
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Statistical analysis description:

Convenience: analysis was performed as described in Statistical Analysis 1. Actual number of subjects included in analysis were 307.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1472
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	7.25

Statistical analysis title	Statistical Analysis 7
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Statistical analysis description:

Global Satisfaction: analysis was performed using MMRM model including treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at baseline (<18 versus ≥18 years old), percent predicted FEV1 severity at Screening (<70 versus ≥70), and baseline TSQM global satisfaction score. Actual number of subjects included in analysis were 317.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0345
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	10.58

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Global Satisfaction: analysis was performed as described in Statistical Analysis 1. Actual number of subjects included in analysis were 307.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0109
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	6.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.55
upper limit	11.89

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

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Treatment-Emergent Serious Adverse Events (SAEs)
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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, in-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. Any AE that increased in severity or that was newly developed at or after the initial dosing of study drug to 28 days after the last dose of study drug is considered treatment-emergent. Safety Set (SS) included all randomized subjects who received any amount of study drug.

End point type	Secondary
End point timeframe:	
up to Week 28	

End point values	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	183	182	
Units: subjects				
number (not applicable)				
Subjects With Treatment-Emergent AEs	174	175	174	
Subjects With Treatment-Emergent SAEs	49	33	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose Concentration (Ctrough), Average Pre-dose Concentration (Ctrough,Avg), 3 to 6 Hours Post-dose Concentration (C3-6h), and Average 3 to 6 Hours Post-dose Concentration (C3-6h,Avg)

End point title	Pre-dose Concentration (Ctrough), Average Pre-dose Concentration (Ctrough,Avg), 3 to 6 Hours Post-dose Concentration (C3-6h), and Average 3 to 6 Hours Post-dose Concentration (C3-6h,Avg) ^[6]
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End point description:

Ctrough, Ctrough,avg, C3-6h, and C3-6h,avg for lumacaftor, M28 lumacaftor (lumacaftor metabolite), ivacaftor, M1 ivacaftor (ivacaftor metabolite), and M6 ivacaftor (ivacaftor metabolite) were calculated. C3-6h,ave is average of individual 3 to 6 hours post-dose observed concentrations across Day 15, and Weeks 4 and 8 and Ctrough,ave is average of individual pre-dose observed concentrations across Weeks 4, 8, and 16. This outcome was not planned to be assessed in Placebo arm. Pharmacokinetic (PK) population included all randomized subjects who received at least one dose of study drug and had a PK assessment. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint and "n" signifies subjects evaluable for specified category for each arm, respectively.

End point type	Secondary
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End point timeframe:

For C3-6h: 3 to 6 hours after morning dose on Day 1 and 15, Week 4 and 8; For C3-6h,avg 3 to 6 hours after morning dose on Day 15, Week 4 and 8; For Ctrough and Ctrough,avg: before morning dose on Week 4, 8, and 16

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: Pharmacokinetic (PK) analysis was not performed in subjects receiving placebo.

End point values	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	181		
Units: microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
LUM, Day 1: C3-6h (n = 180, 175)	27.5 (± 12.5)	18.4 (± 8.55)		
LUM, Day 15: Ctrough (n = 172, 175)	7.56 (± 5.33)	14.1 (± 6.99)		
LUM, Day 15: C3-6 (n = 167, 171)	26.1 (± 11.5)	23.6 (± 8.54)		
LUM, Week 4: Ctrough (n = 172, 178)	7.75 (± 5.05)	13.4 (± 6.7)		
LUM, Week 4: C3-6 (n = 170, 171)	28.4 (± 11.2)	24.2 (± 8.66)		
LUM, Week 8: Ctrough (n = 173, 174)	7.43 (± 5.6)	13.4 (± 6.68)		
LUM, Week 8: C3-6 (n = 165, 171)	28.2 (± 11.2)	24.4 (± 8.8)		
LUM, Week 16: Ctrough (n = 165, 164)	6.95 (± 4.99)	13.5 (± 7.49)		
M-28 LUM, Day 1: C3-6h (n = 180, 175)	0.22 (± 0.107)	0.179 (± 0.0811)		

M-28 LUM, Day 15: Ctrough (n = 172, 175)	1.25 (± 0.614)	1.48 (± 0.59)		
M-28 LUM, Day 15: C3-6 (n = 167, 171)	1.37 (± 0.606)	1.49 (± 0.576)		
M-28 LUM, Week 4: Ctrough (n = 172, 178)	1.31 (± 0.646)	1.48 (± 0.642)		
M-28 LUM, Week 4: C3-6 (n = 170, 171)	1.39 (± 0.635)	1.49 (± 0.615)		
M-28 LUM, Week 8: Ctrough (n = 173, 174)	1.32 (± 0.684)	1.53 (± 0.674)		
M-28 LUM, Week 8: C3-6 (n = 165, 171)	1.42 (± 0.658)	1.56 (± 0.669)		
M-28 LUM, Week 16: Ctrough (n = 165, 164)	1.3 (± 0.769)	1.57 (± 0.757)		
IVA, Day 1: C3-6h (n = 180, 175)	1.29 (± 0.624)	1.24 (± 0.63)		
IVA, Day 15: Ctrough (n = 172, 176)	0.151 (± 0.123)	0.115 (± 0.123)		
IVA, Day 15: C3-6 (n = 167, 171)	0.557 (± 0.311)	0.413 (± 0.199)		
IVA, Week 4: Ctrough (n = 172, 178)	0.142 (± 0.107)	0.105 (± 0.083)		
IVA, Week 4: C3-6 (n = 170, 171)	0.638 (± 0.325)	0.456 (± 0.235)		
IVA, Week 8: Ctrough (n = 173, 174)	0.13 (± 0.101)	0.0894 (± 0.0726)		
IVA, Week 8: C3-6 (n = 165, 171)	0.648 (± 0.364)	0.47 (± 0.295)		
IVA, Week 16: Ctrough (n = 165, 164)	0.133 (± 0.131)	0.0834 (± 0.0622)		
M-1 IVA, Day 1: C3-6h (n = 180, 175)	2.46 (± 1.29)	2.41 (± 1.35)		
M-1 IVA, Day 15: Ctrough (n = 172, 176)	0.665 (± 0.578)	0.511 (± 0.53)		
M-1 IVA, Day 15: C3-6 (n = 167, 171)	1.94 (± 0.981)	1.71 (± 0.867)		
M-1 IVA, Week 4: Ctrough (n = 172, 178)	0.628 (± 0.492)	0.45 (± 0.345)		
M-1 IVA, Week 4: C3-6 (n = 170, 171)	2.21 (± 1.01)	1.76 (± 0.932)		
M-1 IVA, Week 8: Ctrough (n = 173, 174)	0.584 (± 0.451)	0.404 (± 0.381)		
M-1 IVA, Week 8: C3-6 (n = 165, 171)	2.17 (± 1.06)	1.78 (± 0.975)		
M-1 IVA, Week 16: Ctrough (n = 165, 164)	0.589 (± 0.519)	0.396 (± 0.319)		
M-6 IVA, Day 1: C3-6h (n = 180, 175)	0.976 (± 0.877)	0.927 (± 0.875)		
M-6 IVA, Day 15: Ctrough (n = 172, 176)	1.68 (± 1.31)	1.67 (± 1.4)		
M-6 IVA, Day 15: C3-6 (n = 167, 171)	3.03 (± 1.96)	2.87 (± 1.81)		
M-6 IVA, Week 4: Ctrough (n = 172, 178)	1.66 (± 1.36)	1.46 (± 0.938)		
M-6 IVA, Week 4: C3-6 (n = 170, 171)	3.07 (± 1.92)	2.49 (± 1.53)		
M-6 IVA, Week 8: Ctrough (n = 173, 174)	1.52 (± 1.12)	1.31 (± 0.946)		
M-6 IVA, Week 8: C3-6 (n = 165, 171)	2.96 (± 1.86)	2.36 (± 1.57)		
M-6 IVA, Week 16: Ctrough (n = 165, 164)	1.4 (± 1.11)	1.33 (± 1.02)		
LUM: Ctrough,ave (n = 179, 181)	7.49 (± 3.93)	13.5 (± 5.52)		
LUM: C3-6h, ave (n = 179, 181)	27.7 (± 8.63)	24 (± 7.29)		
M-28 LUM: Ctrough,ave (n = 179, 181)	1.31 (± 0.628)	1.51 (± 0.614)		
M-28 LUM: C3-6h, ave (n = 179, 181)	1.39 (± 0.596)	1.51 (± 0.585)		
IVA: Ctrough,ave (n = 179, 181)	0.137 (± 0.0773)	0.0989 (± 0.0644)		

IVA: C3-6h, ave (n = 179, 181)	0.614 (± 0.271)	0.445 (± 0.193)		
M1-IVA: Ctrough,ave (n = 179, 181)	0.606 (± 0.35)	0.441 (± 0.293)		
M1-IVA: C3-6h, ave (n = 179, 181)	2.11 (± 0.817)	1.74 (± 0.726)		
M6-IVA: Ctrough,ave (n = 179, 181)	1.57 (± 0.992)	1.44 (± 0.861)		
M6-IVA: C3-6h, ave (n = 179, 181)	3.04 (± 1.55)	2.57 (± 1.34)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to Week 28

Adverse event reporting additional description:

Subjects were analyzed as per actual treatment received. Other adverse events includes only nonserious AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo matched to lumacaftor (LUM, VX-809) and ivacaftor (IVA, VX-770) tablet every 12 hours (q12h), up to Week 24.

Reporting group title	LUM 600 mg qd/IVA 250 mg q12h
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Reporting group description:

LUM 600 mg plus IVA 250 mg supplied as fixed-dose combination (FDC) tablet in the morning and IVA 250 mg film-coated tablet in the evening, up to Week 24.

Reporting group title	LUM 400 mg q12h/ IVA 250 mg q12h
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Reporting group description:

LUM 400 mg plus IVA 250 mg supplied as FDC tablet in the morning and in the evening, up to Week 24.

Serious adverse events	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/ IVA 250 mg q12h
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 184 (26.63%)	33 / 183 (18.03%)	33 / 182 (18.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer metastatic			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (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
Renal cancer			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (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
Seminoma			

subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Implant site thrombosis			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	5 / 182 (2.75%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Lung disorder			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
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 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	2 / 184 (1.09%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal adhesions			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Dysphagia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Inguinal hernia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Vomiting			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 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	41 / 184 (22.28%)	19 / 183 (10.38%)	17 / 182 (9.34%)
occurrences causally related to treatment / all	1 / 51	0 / 22	0 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (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
Bronchopneumonia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (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
Catheter site cellulitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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

Clostridium difficile infection			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Gastroenteritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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 exacerbation of bronchiectasis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (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
Kidney infection			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Respiratory tract infection viral			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Urinary tract infection			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetes mellitus inadequate control subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (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

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

Non-serious adverse events	Placebo	LUM 600 mg qd/IVA 250 mg q12h	LUM 400 mg q12h/ IVA 250 mg q12h
Total subjects affected by non-serious adverse events			
subjects affected / exposed	173 / 184 (94.02%)	175 / 183 (95.63%)	172 / 182 (94.51%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	0	2	2
Flushing			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Hot flush			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	0	0	2
Deep vein thrombosis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Poor venous access			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 184 (10.33%)	17 / 183 (9.29%)	17 / 182 (9.34%)
occurrences (all)	20	17	18
Pyrexia			

subjects affected / exposed	12 / 184 (6.52%)	12 / 183 (6.56%)	17 / 182 (9.34%)
occurrences (all)	14	14	19
Asthenia			
subjects affected / exposed	3 / 184 (1.63%)	5 / 183 (2.73%)	3 / 182 (1.65%)
occurrences (all)	3	5	3
Pain			
subjects affected / exposed	2 / 184 (1.09%)	4 / 183 (2.19%)	3 / 182 (1.65%)
occurrences (all)	2	4	3
Chest discomfort			
subjects affected / exposed	1 / 184 (0.54%)	3 / 183 (1.64%)	3 / 182 (1.65%)
occurrences (all)	1	4	3
Malaise			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	1	4	3
Chills			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	1	0	2
Drug intolerance			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	3 / 182 (1.65%)
occurrences (all)	0	0	3
Chest pain			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Drug interaction			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	2
Exercise tolerance decreased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Feeling abnormal			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Feeling cold			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Feeling hot			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Hyperthermia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Implant site thrombosis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Local swelling			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Medical device pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Seasonal allergy			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Anaphylactic reaction			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Hypersensitivity			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Milk allergy			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	2	3	3
Metrorrhagia			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	0	3	3
Amenorrhoea			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	3 / 182 (1.65%)
occurrences (all)	0	0	4
Menorrhagia			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	0	2	1
Menstruation irregular			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	0	3	1
Polymenorrhoea			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Erectile dysfunction			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Gynaecomastia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Penile erythema			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Testicular pain			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	66 / 184 (35.87%)	52 / 183 (28.42%)	47 / 182 (25.82%)
occurrences (all)	93	63	60
Haemoptysis			

subjects affected / exposed	23 / 184 (12.50%)	22 / 183 (12.02%)	26 / 182 (14.29%)
occurrences (all)	29	27	34
Sputum increased			
subjects affected / exposed	23 / 184 (12.50%)	15 / 183 (8.20%)	25 / 182 (13.74%)
occurrences (all)	25	16	27
Dyspnoea			
subjects affected / exposed	14 / 184 (7.61%)	21 / 183 (11.48%)	17 / 182 (9.34%)
occurrences (all)	15	29	23
Respiration abnormal			
subjects affected / exposed	9 / 184 (4.89%)	26 / 183 (14.21%)	14 / 182 (7.69%)
occurrences (all)	10	32	16
Nasal congestion			
subjects affected / exposed	25 / 184 (13.59%)	9 / 183 (4.92%)	11 / 182 (6.04%)
occurrences (all)	29	9	12
Oropharyngeal pain			
subjects affected / exposed	10 / 184 (5.43%)	24 / 183 (13.11%)	11 / 182 (6.04%)
occurrences (all)	14	26	12
Rhinorrhoea			
subjects affected / exposed	5 / 184 (2.72%)	6 / 183 (3.28%)	10 / 182 (5.49%)
occurrences (all)	6	6	10
Wheezing			
subjects affected / exposed	6 / 184 (3.26%)	5 / 183 (2.73%)	5 / 182 (2.75%)
occurrences (all)	6	7	8
Rales			
subjects affected / exposed	7 / 184 (3.80%)	4 / 183 (2.19%)	4 / 182 (2.20%)
occurrences (all)	7	5	5
Productive cough			
subjects affected / exposed	1 / 184 (0.54%)	6 / 183 (3.28%)	7 / 182 (3.85%)
occurrences (all)	1	8	7
Respiratory tract congestion			
subjects affected / exposed	5 / 184 (2.72%)	3 / 183 (1.64%)	4 / 182 (2.20%)
occurrences (all)	6	3	5
Epistaxis			
subjects affected / exposed	4 / 184 (2.17%)	4 / 183 (2.19%)	2 / 182 (1.10%)
occurrences (all)	5	11	2
Asthma			

subjects affected / exposed	3 / 184 (1.63%)	0 / 183 (0.00%)	6 / 182 (3.30%)
occurrences (all)	4	0	6
Bronchospasm			
subjects affected / exposed	1 / 184 (0.54%)	3 / 183 (1.64%)	5 / 182 (2.75%)
occurrences (all)	1	3	6
Sinus congestion			
subjects affected / exposed	1 / 184 (0.54%)	7 / 183 (3.83%)	1 / 182 (0.55%)
occurrences (all)	1	7	1
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 184 (0.54%)	4 / 183 (2.19%)	3 / 182 (1.65%)
occurrences (all)	1	4	3
Sputum discoloured			
subjects affected / exposed	3 / 184 (1.63%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	3	2	1
Nasal inflammation			
subjects affected / exposed	1 / 184 (0.54%)	3 / 183 (1.64%)	1 / 182 (0.55%)
occurrences (all)	1	3	1
Rhinitis allergic			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	2	1	2
Rhonchi			
subjects affected / exposed	2 / 184 (1.09%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	2	2	1
Upper-airway cough syndrome			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	3	1	2
Dysphonia			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	2	1	1
Dyspnoea exertional			
subjects affected / exposed	0 / 184 (0.00%)	3 / 183 (1.64%)	1 / 182 (0.55%)
occurrences (all)	0	3	1
Increased upper airway secretion			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	1	1	2
Increased viscosity of bronchial			

secretion			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	2	0	2
Painful respiration			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	2	1	1
Pharyngeal erythema			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	1	2	1
Pleuritic pain			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	2	0	2
Lung hyperinflation			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	1	2	1
Throat irritation			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	3	0	1
Bronchial hyperreactivity			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Nasal polyps			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Obstructive airways disorder			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Paranasal cyst			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Pulmonary congestion			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	0	2	0
Allergic cough			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0

Bronchial obstruction			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	2
Bronchiectasis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Nasal obstruction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Nasal oedema			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Nasal septum deviation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Pharyngeal exudate			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Prolonged expiration			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Pulmonary pain			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Respiratory failure			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Respiratory tract irritation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1

Rhinalgia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Sneezing			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Throat tightness			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 184 (3.26%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	8	2	3
Anxiety			
subjects affected / exposed	2 / 184 (1.09%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	2	2	2
Depression			
subjects affected / exposed	4 / 184 (2.17%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	4	1	1
Depressed mood			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	3 / 182 (1.65%)
occurrences (all)	0	0	3
Irritability			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Attention deficit/hyperactivity disorder			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Bradyphrenia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Depressive symptom			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Disorientation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Disturbance in social behaviour			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Emotional disorder			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Libido decreased			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Middle insomnia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Suicidal ideation			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	10 / 184 (5.43%)	10 / 183 (5.46%)	13 / 182 (7.14%)
occurrences (all)	11	12	14
Bacterial test positive			
subjects affected / exposed	9 / 184 (4.89%)	4 / 183 (2.19%)	7 / 182 (3.85%)
occurrences (all)	13	6	9
Alanine aminotransferase increased			
subjects affected / exposed	5 / 184 (2.72%)	4 / 183 (2.19%)	3 / 182 (1.65%)
occurrences (all)	5	4	4
Forced expiratory volume decreased			

subjects affected / exposed	7 / 184 (3.80%)	3 / 183 (1.64%)	1 / 182 (0.55%)
occurrences (all)	7	3	1
Weight decreased			
subjects affected / exposed	5 / 184 (2.72%)	2 / 183 (1.09%)	4 / 182 (2.20%)
occurrences (all)	5	2	4
Liver function test abnormal			
subjects affected / exposed	6 / 184 (3.26%)	3 / 183 (1.64%)	1 / 182 (0.55%)
occurrences (all)	7	3	1
Pulmonary function test decreased			
subjects affected / exposed	6 / 184 (3.26%)	4 / 183 (2.19%)	0 / 182 (0.00%)
occurrences (all)	7	4	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 184 (1.63%)	3 / 183 (1.64%)	3 / 182 (1.65%)
occurrences (all)	3	3	4
Blood creatinine increased			
subjects affected / exposed	4 / 184 (2.17%)	3 / 183 (1.64%)	1 / 182 (0.55%)
occurrences (all)	4	3	1
White blood cell count increased			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	1	2	2
Blood glucose decreased			
subjects affected / exposed	3 / 184 (1.63%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	3	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	0	2	2
Vitamin D decreased			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	1	1	2
Breath sounds abnormal			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	1	2	0
Fungal test positive			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	1	1	1

Staphylococcus test positive subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	2 / 182 (1.10%) 2
Transaminases increased subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	1 / 183 (0.55%) 1	1 / 182 (0.55%) 1
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 184 (1.09%) 2	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Blood glucose increased subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Blood immunoglobulin E increased subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Blood phosphorus increased subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Body temperature increased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	1 / 182 (0.55%) 1
Atypical mycobacterium test positive subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Blood calcium increased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Blood phosphorus abnormal			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Blood potassium increased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Blood sodium decreased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	2
Blood urea increased			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Chest X-ray abnormal			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Forced expiratory volume increased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Glucose tolerance test abnormal			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Glucose urine present			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Haemoglobin increased			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Heart rate increased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0

Neutrophil count increased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Pseudomonas test positive subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Red blood cell count increased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Sputum abnormal subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Urine calcium increased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Vitamin E decreased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Injury, poisoning and procedural complications			
Muscle strain subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	3 / 183 (1.64%) 4	2 / 182 (1.10%) 2
Joint injury subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	1 / 183 (0.55%) 1	2 / 182 (1.10%) 2
Ligament sprain			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	0	1	2
Procedural pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	1	0	2
Concussion			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	0	0	2
Excoriation			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	3	0	0
Facial bones fracture			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	2	0	0
Stoma site pain			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	0	3	0
Sunburn			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Arthropod bite			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Back injury			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Foreign body in eye			

subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Meniscus injury			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Muscle rupture			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Post procedural complication			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Radius fracture			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Skeletal injury			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Stoma site erythema			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Vaccination complication			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Vascular procedure complication			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			

subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	2 / 183 (1.09%) 2	0 / 182 (0.00%) 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Atrial fibrillation			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block second degree			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Defect conduction intraventricular			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Pericarditis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 184 (13.59%)	28 / 183 (15.30%)	29 / 182 (15.93%)
occurrences (all)	29	42	35
Dizziness			
subjects affected / exposed	5 / 184 (2.72%)	5 / 183 (2.73%)	5 / 182 (2.75%)
occurrences (all)	6	5	6
Sinus headache			
subjects affected / exposed	2 / 184 (1.09%)	3 / 183 (1.64%)	3 / 182 (1.65%)
occurrences (all)	2	5	3
Migraine			
subjects affected / exposed	3 / 184 (1.63%)	0 / 183 (0.00%)	3 / 182 (1.65%)
occurrences (all)	3	0	4
Lethargy			

subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	1	2	2
Dysgeusia			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	2	0	2
Poor quality sleep			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	3 / 182 (1.65%)
occurrences (all)	0	0	3
Dysarthria			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Paraesthesia			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	0	2	0
Syncope			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Tremor			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	0	0	5
Amnesia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Ataxia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Dysaesthesia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Epilepsy			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Hypoaesthesia			

subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Tension headache			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	1	2	0
Lymphadenopathy			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	1	2	0
Lymph node pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Thrombocytosis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 184 (0.54%)	4 / 183 (2.19%)	0 / 182 (0.00%)
occurrences (all)	1	5	0
Ear pain			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	1	2	1
Cerumen impaction			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	0	2	0
Tympanic membrane disorder			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Ear canal erythema			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Ear congestion			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	1	1	2
Asthenopia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Blepharospasm			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Astigmatism			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis allergic			

subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Eye disorder			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Visual acuity reduced			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 184 (7.07%)	16 / 183 (8.74%)	24 / 182 (13.19%)
occurrences (all)	14	19	34
Abdominal pain			
subjects affected / exposed	12 / 184 (6.52%)	11 / 183 (6.01%)	23 / 182 (12.64%)
occurrences (all)	15	17	31
Nausea			
subjects affected / exposed	11 / 184 (5.98%)	9 / 183 (4.92%)	14 / 182 (7.69%)
occurrences (all)	12	11	18
Constipation			
subjects affected / exposed	11 / 184 (5.98%)	6 / 183 (3.28%)	7 / 182 (3.85%)
occurrences (all)	11	7	7
Abdominal pain upper			
subjects affected / exposed	10 / 184 (5.43%)	7 / 183 (3.83%)	5 / 182 (2.75%)
occurrences (all)	11	8	8
Flatulence			
subjects affected / exposed	1 / 184 (0.54%)	9 / 183 (4.92%)	11 / 182 (6.04%)
occurrences (all)	1	11	11
Vomiting			
subjects affected / exposed	2 / 184 (1.09%)	8 / 183 (4.37%)	7 / 182 (3.85%)
occurrences (all)	2	9	8
Abdominal distension			
subjects affected / exposed	4 / 184 (2.17%)	2 / 183 (1.09%)	5 / 182 (2.75%)
occurrences (all)	4	3	6

Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 184 (1.09%)	3 / 183 (1.64%)	6 / 182 (3.30%)
occurrences (all)	2	3	6
Dyspepsia			
subjects affected / exposed	2 / 184 (1.09%)	3 / 183 (1.64%)	4 / 182 (2.20%)
occurrences (all)	2	4	4
Abdominal discomfort			
subjects affected / exposed	1 / 184 (0.54%)	3 / 183 (1.64%)	3 / 182 (1.65%)
occurrences (all)	1	3	3
Enteritis			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	3 / 182 (1.65%)
occurrences (all)	2	0	3
Steatorrhoea			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	3 / 182 (1.65%)
occurrences (all)	0	1	3
Dry mouth			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	1	1	1
Frequent bowel movements			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	1	1	1
Toothache			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	1	0	2
Abdominal pain lower			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	0	2	0
Faeces soft			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Gastrointestinal motility disorder			

subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Malabsorption			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Abdominal tenderness			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Anal fissure			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Chapped lips			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Colonic haematoma			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Defaecation urgency			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Faecaloma			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Gastric dilatation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			

subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Gingivitis ulcerative			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Oesophagitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Rectal tenesmus			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Tongue coated			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Hepatitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 184 (1.09%)	8 / 183 (4.37%)	6 / 182 (3.30%)
occurrences (all)	2	8	6
Pruritus			
subjects affected / exposed	1 / 184 (0.54%)	5 / 183 (2.73%)	4 / 182 (2.20%)
occurrences (all)	1	6	5
Acne			

subjects affected / exposed	5 / 184 (2.72%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	5	1	1
Hyperhidrosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	0	1	2
Night sweats			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	0	3	1
Urticaria			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	2	1	0
Alopecia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Dermatitis allergic			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	2	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	0	0	2
Pruritus allergic			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Pruritus generalised			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Rash macular			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Chloasma			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Cold sweat			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			

subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Drug eruption			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Erythema nodosum			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Macule			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Rash generalised			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	2
Red man syndrome			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	1	2	0

Urine odour abnormal subjects affected / exposed occurrences (all)	2 / 184 (1.09%) 2	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Calculus urinary subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Haematuria subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Leukocyturia subjects affected / exposed occurrences (all)	1 / 184 (0.54%) 1	0 / 183 (0.00%) 0	0 / 182 (0.00%) 0
Nephropathy subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Nephropathy toxic subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Pollakiuria subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Renal failure acute subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Urine abnormality subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	0 / 183 (0.00%) 0	1 / 182 (0.55%) 1
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 184 (0.00%) 0	1 / 183 (0.55%) 1	0 / 182 (0.00%) 0
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	6 / 184 (3.26%) 6	7 / 183 (3.83%) 7	3 / 182 (1.65%) 3
Myalgia			

subjects affected / exposed	4 / 184 (2.17%)	3 / 183 (1.64%)	7 / 182 (3.85%)
occurrences (all)	5	3	7
Back pain			
subjects affected / exposed	5 / 184 (2.72%)	3 / 183 (1.64%)	5 / 182 (2.75%)
occurrences (all)	6	3	6
Arthralgia			
subjects affected / exposed	4 / 184 (2.17%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	4	1	2
Pain in extremity			
subjects affected / exposed	4 / 184 (2.17%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	4	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	3 / 182 (1.65%)
occurrences (all)	0	1	3
Flank pain			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	0	2	1
Muscle spasms			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	2	1	0
Joint swelling			
subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1
Tendon pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Arthropathy			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Intervertebral disc protrusion			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal discomfort			

subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Tendon disorder			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	58 / 184 (31.52%)	57 / 183 (31.15%)	54 / 182 (29.67%)
occurrences (all)	86	79	75
Nasopharyngitis			
subjects affected / exposed	20 / 184 (10.87%)	9 / 183 (4.92%)	26 / 182 (14.29%)
occurrences (all)	23	13	33
Upper respiratory tract infection			
subjects affected / exposed	10 / 184 (5.43%)	16 / 183 (8.74%)	17 / 182 (9.34%)
occurrences (all)	13	21	21
Rhinitis			
subjects affected / exposed	12 / 184 (6.52%)	16 / 183 (8.74%)	8 / 182 (4.40%)
occurrences (all)	17	18	8
Sinusitis			
subjects affected / exposed	12 / 184 (6.52%)	7 / 183 (3.83%)	5 / 182 (2.75%)
occurrences (all)	15	7	5
Influenza			
subjects affected / exposed	3 / 184 (1.63%)	8 / 183 (4.37%)	8 / 182 (4.40%)
occurrences (all)	3	8	8
Bronchitis			
subjects affected / exposed	7 / 184 (3.80%)	9 / 183 (4.92%)	2 / 182 (1.10%)
occurrences (all)	11	11	4
Respiratory tract infection			

subjects affected / exposed	3 / 184 (1.63%)	2 / 183 (1.09%)	6 / 182 (3.30%)
occurrences (all)	5	2	7
Pharyngitis			
subjects affected / exposed	2 / 184 (1.09%)	4 / 183 (2.19%)	4 / 182 (2.20%)
occurrences (all)	2	4	4
Vulvovaginal mycotic infection			
subjects affected / exposed	4 / 184 (2.17%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	4	2	5
Oral candidiasis			
subjects affected / exposed	3 / 184 (1.63%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	3	3	3
Urinary tract infection			
subjects affected / exposed	3 / 184 (1.63%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	3	2	3
Upper respiratory tract infection bacterial			
subjects affected / exposed	2 / 184 (1.09%)	2 / 183 (1.09%)	3 / 182 (1.65%)
occurrences (all)	3	3	3
Viral infection			
subjects affected / exposed	4 / 184 (2.17%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	4	2	1
Gastroenteritis viral			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	1	2	2
Lower respiratory tract infection bacterial			
subjects affected / exposed	3 / 184 (1.63%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	3	1	1
Respiratory tract infection viral			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	2 / 182 (1.10%)
occurrences (all)	1	2	2
Gastroenteritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	3 / 182 (1.65%)
occurrences (all)	0	1	3
H1N1 influenza			

subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	1	1	2
Oral herpes			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	2 / 182 (1.10%)
occurrences (all)	1	1	2
Otitis media			
subjects affected / exposed	0 / 184 (0.00%)	3 / 183 (1.64%)	1 / 182 (0.55%)
occurrences (all)	0	3	1
Acute sinusitis			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	2	1	1
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	1	2	0
Fungal skin infection			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	2	1	0
Laryngitis			
subjects affected / exposed	1 / 184 (0.54%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	1	2	0
Sputum purulent			
subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	1 / 182 (0.55%)
occurrences (all)	0	2	1
Bacterial disease carrier			
subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Chronic sinusitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	2	1
Clostridium difficile colitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Herpes zoster			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1

Lower respiratory tract infection viral subjects affected / exposed	0 / 184 (0.00%)	2 / 183 (1.09%)	0 / 182 (0.00%)
occurrences (all)	0	3	0
Mycobacterium abscessus infection subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	2	0	0
Pharyngitis streptococcal subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Tonsillitis subjects affected / exposed	1 / 184 (0.54%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	1	1	0
Vulvovaginal candidiasis subjects affected / exposed	2 / 184 (1.09%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	2	0	0
Acute tonsillitis subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Body tinea subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Bronchopulmonary aspergillosis subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis bacterial subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Ear infection subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Eye infection subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Folliculitis subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1

Genital infection fungal			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Giardiasis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Herpes dermatitis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Lung infection			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Lung infection pseudomonal			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Oral fungal infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	2
Otitis externa			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Overgrowth bacterial			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Pseudomonas bronchitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	2	0

Soft tissue infection			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Stoma site infection			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Subcutaneous abscess			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Tinea pedis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Tinea versicolour			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Vestibular neuronitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Viral rhinitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Viral tonsillitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	12 / 184 (6.52%)	15 / 183 (8.20%)	13 / 182 (7.14%)
occurrences (all)	15	19	19
Bronchitis bacterial			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	0	1	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 184 (2.17%)	6 / 183 (3.28%)	6 / 182 (3.30%)
occurrences (all)	4	6	6
Hypoglycaemia			
subjects affected / exposed	3 / 184 (1.63%)	6 / 183 (3.28%)	2 / 182 (1.10%)
occurrences (all)	3	6	3
Dehydration			
subjects affected / exposed	3 / 184 (1.63%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	3	0	1
Hyperglycaemia			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences (all)	2	1	1
Gout			
subjects affected / exposed	2 / 184 (1.09%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	2	1	0
Diabetes mellitus			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	1	0	1
Hyponatraemia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	2 / 182 (1.10%)
occurrences (all)	0	0	2
Glucose tolerance impaired			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	1 / 184 (0.54%)	0 / 183 (0.00%)	0 / 182 (0.00%)
occurrences (all)	1	0	0
Magnesium deficiency			

subjects affected / exposed	0 / 184 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
occurrences (all)	0	0	1
Vitamin K deficiency			
subjects affected / exposed	0 / 184 (0.00%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2013	Modified primary endpoint and selected secondary endpoint.
05 February 2014	Order of primary and key secondary endpoints was revised.
24 February 2014	Clarification on which subjects were required to complete the Safety Follow-up Visit was provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported