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

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2012-003990-24
Trial protocol	BE DE AT GB ES DK
Global end of trial date	25 April 2014

Results information

Result version number	v2 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Address EudraCT System related issues & verify data

Trial information

Trial identification

Sponsor protocol code	VX12-809-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01807949
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)	EMEA-001582-PIP01-13
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 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 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	11 April 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	Australia: 42
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 335
Worldwide total number of subjects	559
EEA total number of subjects	168

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)	132
Adults (18-64 years)	427
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 187, 187, and 189 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 187, 185, and 187 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 400 mg q12h/IVA 250 mg q12h

Arm description:

LUM 400 milligram (mg) plus IVA 250 mg supplied as fixed-dose combination (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.

Arm title	LUM 600 mg qd/IVA 250 mg q12h

Arm description:

LUM 600 mg plus IVA 250 mg supplied as 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.

Number of subjects in period 1	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h
Started	187	187	185
Completed	185	180	180
Not completed	2	7	5
Consent withdrawn by subject	1	2	2
Non-Compliance	-	1	-
Undefined	-	2	1
Adverse Events	1	2	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 400 mg q12h/IVA 250 mg q12h
Reporting group description:	
LUM 400 milligram (mg) plus IVA 250 mg supplied as fixed-dose combination (FDC) tablets in the morning and in the evening, up to Week 24.	
Reporting group title	LUM 600 mg qd/IVA 250 mg q12h
Reporting group description:	
LUM 600 mg plus IVA 250 mg supplied as FDC tablets in the morning and IVA 250 mg film-coated tablet in the evening, up to Week 24.	

Reporting group values	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h
Number of subjects	187	187	185
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	25.7	25	24.3
standard deviation	± 10.02	± 9.03	± 8.31
Gender categorical Units: Subjects			
Female	97	98	96
Male	90	89	89

Reporting group values	Total		
Number of subjects	559		
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	291		
Male	268		

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 400 mg q12h/IVA 250 mg q12h
Reporting group description:	
LUM 400 milligram (mg) plus IVA 250 mg supplied as fixed-dose combination (FDC) tablets in the morning and in the evening, up to Week 24.	
Reporting group title	LUM 600 mg qd/IVA 250 mg q12h
Reporting group description:	
LUM 600 mg plus IVA 250 mg supplied as FDC tablets in the morning and IVA 250 mg film-coated tablet 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 subject 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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	180	181	
Units: percent predicted of FEV1				
least squares mean (standard error)	-0.15 (± 0.539)	2.85 (± 0.54)	2.46 (± 0.54)	

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 (<18 versus >=18 years old), and percent predicted FEV1 severity at Screening (<70 versus >=70).

Comparison groups	Placebo v LUM 600 mg qd/IVA 250 mg q12h
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Mixed-Effects Model for Repeated Measure
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	4.06

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	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	4.44

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:

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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	180	181	
Units: percent change				
least squares mean (standard error)	0 (± 0.96)	5.25 (± 0.961)	4.42 (± 0.961)	

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), 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	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	4.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.86
upper limit	6.98

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	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	5.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.69
upper limit	7.81

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

End point description:

BMI was defined as weight in kilogram (kg) divided by height*height in square meter (m^2). 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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	180	180	
Units: kilogram per square meter (kg/m^2)				
least squares mean (standard error)	0.07 (± 0.066)	0.43 (± 0.066)	0.48 (± 0.066)	

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 BMI.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.59

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	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.54

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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	179	180	
Units: units on a scale				
least squares mean (standard error)	2.81 (± 1.153)	5.66 (± 1.169)	5.02 (± 1.166)	

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	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1651
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	5.33

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	364
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0736
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	2.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	5.98

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 >=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. 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. Analysis was performed on FAS

End point type	Secondary

End point timeframe:

Week 16 and 24

End point values	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	187	185	
Units: percentage of subjects				
number (not applicable)	22.5	41.2	45.9	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.9568
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8829
upper limit	4.6431

Notes:

[1] - 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 as described in Statistical Analysis 1.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.3834
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5234
upper limit	3.7286

Notes:

[2] - 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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	187	185	
Units: pulmonary exacerbation events per year				
number (not applicable)	1.18	0.67	0.82	

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	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0116 [3]
Method	Negative Binomial Regression
Parameter estimate	Event Rate Ratio
Point estimate	0.6912
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5187
upper limit	0.9209

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

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	374
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0002
Method	Negative Binomial Regression
Parameter estimate	Event Rate Ratio
Point estimate	0.5659
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4191
upper limit	0.7641

Notes:

[4] - 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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	180	180	
Units: kilograms (kg)				
least squares mean (standard error)	0.44 (± 0.187)	1.38 (± 0.187)	1.57 (± 0.188)	

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	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.64

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	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.46

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 subject 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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	58	54	
Units: z-score				
least squares mean (standard error)	-0.0674 (± 0.04706)	0.1544 (± 0.04513)	0.164 (± 0.04652)	

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 BMI z-score.

Comparison groups	Placebo v LUM 600 mg qd/IVA 250 mg q12h
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.2313
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1037
upper limit	0.3589

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	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.2217
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0961
upper limit	0.3473

Secondary: Time-to-First Pulmonary Exacerbation

End point title	Time-to-First Pulmonary Exacerbation

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. 99999 indicates median time was not reached as less than 50% of subjects had the event of interest. 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

End point timeframe:

Through Week 24

End point values	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	187	185	
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

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
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0384
Method	Cox Proportional Hazard Regression

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	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
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. Here, number of participants analyzed signifies participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Through Week 24

End point values	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	187	185	
Units: percentage of subjects				
number (not applicable)	47.1	28.9	36.8	

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	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0393
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.6373
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.416
upper limit	0.9764

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	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.4429
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2863
upper limit	0.6851

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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	183	176	178	
Units: units on a scale				
least squares mean (standard error)	0.0117 (± 0.00673)	0.0108 (± 0.00683)	0.009 (± 0.00682)	

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 EQ-5D-3L index score.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7679
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.0028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0211
upper limit	0.0156

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	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9214
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.0009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0192
upper limit	0.0174

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 Week

	24

End point description:

The EQ-5D-3L VAS records the subject's 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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	182	177	177	
Units: units on a scale				
least squares mean (standard error)	3.3 (± 1.07)	6.6 (± 1.08)	5.7 (± 1.08)	

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 EQ-5D-3L VAS score.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1034
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	5.3

Statistical analysis title	Statistical Analysis 2

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	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0262
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	6.2

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

End point description:

The TSQM is a 14-item self-administered questionnaire which measures subject's experiences with their medication on four dimensions: effectiveness, side effects, convenience and global satisfaction. For each dimension, responses are added and transformed to a scale from 0 to 100, where higher scores indicate greater satisfaction. Analysis was performed on FAS. Here, "n" signifies subjects who were evaluable for specified category for each arm, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	187	187	185	
Units: units on a scale				
least squares mean (standard error)				
Effectiveness (n = 159, 161, 161)	-8.49 (± 1.814)	3.12 (± 1.793)	0.15 (± 1.807)	
Side Effects (n = 157, 161, 159)	2.03 (± 1.144)	-2.26 (± 1.121)	-1.14 (± 1.137)	
Convenience (n = 158, 161, 160)	4.57 (± 1.525)	4.88 (± 1.501)	4.57 (± 1.523)	
Global Satisfaction (n= 158, 161, 160)	-9.62 (± 1.841)	-2.46 (± 1.814)	-4.98 (± 1.845)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

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 320.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	8.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.77
upper limit	13.51

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 320.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	11.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.75
upper limit	16.48

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	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0403
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.21
upper limit	-0.14

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Side Effects: analysis was performed as described in Statistical Analysis 1. Actual number of subjects included in analysis were 318.	
Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-4.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.31
upper limit	-1.28

Statistical analysis title	Statistical Analysis 5
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 318.	
Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.07
upper limit	4.07

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Convenience: analysis was performed as described in Statistical Analysis 1. Actual number of subjects included in analysis were 319.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8777
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.74
upper limit	4.37

Statistical analysis title	Statistical Analysis 7

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 318.

Comparison groups	LUM 600 mg qd/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0668
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	4.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	9.61

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 319.

Comparison groups	LUM 400 mg q12h/IVA 250 mg q12h v Placebo
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	7.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.23
upper limit	12.08

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)

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. Analysis done on Safety Set(SS) included all randomized subjects who received any amount of study drug. Subjects were analyzed as per actual treatment received. Any AE that increased in severity or newly developed at or after the initial dosing of study drug to 28 days after the last dose is TEAE.

End point type	Secondary

End point timeframe:

Up to Week 28

End point values	Placebo	LUM 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	186	187	185[5]	
Units: subjects				
number (not applicable)				
Subjects With Treatment-Emergent AEs	181	177	181	
Subjects With Treatment-Emergent SAEs	57	31	51	

Notes:

[5] - Actual Number of Subjects Analyzed as per Actual Treatment Received = 186

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]

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 endpoint was not planned to be assessed in Placebo arm. Analysis was performed on 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

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 400 mg q12h/IVA 250 mg q12h	LUM 600 mg qd/IVA 250 mg q12h		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	182		
Units: microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
LUM, Day 1: C3-6h (n = 180, 181)	20.2 (± 8.33)	30.8 (± 12.6)		
LUM, Day 15: C3-6h (n = 176, 174)	23.9 (± 8.87)	30.4 (± 11.2)		
LUM, Week 4: Ctrough (n = 179, 174)	13.2 (± 6.28)	8.11 (± 5.21)		
LUM, Week 4: C3-6h (n = 168, 164)	24.5 (± 8.75)	29.2 (± 12.1)		
LUM, Week 8: Ctrough (n = 177, 177)	12.4 (± 6.87)	7.87 (± 5.71)		
LUM, Week 8: C3-6h (n = 170, 174)	24.9 (± 9.79)	30.4 (± 11.6)		
LUM, Week 16: Ctrough (n = 173, 171)	12.2 (± 6.87)	7.53 (± 6.05)		
M-28 LUM, Day 1: C3-6h (n = 180, 181)	0.181 (± 0.079)	0.226 (± 0.103)		
M-28 LUM, Day 15: C3-6h (n = 176, 174)	1.39 (± 0.606)	1.43 (± 0.588)		
M-28 LUM, Week 4: Ctrough (n = 179, 174)	1.42 (± 0.661)	1.32 (± 0.68)		

M-28 LUM, Week 4: C3-6h (n = 168, 164)	1.45 (± 0.675)	1.39 (± 0.657)		
M-28 LUM, Week 8: Ctrough (n = 177, 177)	1.44 (± 0.722)	1.34 (± 0.714)		
M-28 LUM, Week 8: C3-6h (n = 170, 174)	1.48 (± 0.711)	1.41 (± 0.702)		
M-28 LUM, Week 16: Ctrough (n = 173, 171)	1.43 (± 0.775)	1.27 (± 0.763)		
IVA, Day 1: C3-6h (n = 180, 181)	1.36 (± 0.647)	1.34 (± 0.643)		
IVA, Day 15: C3-6h (n = 176, 174)	0.469 (± 0.282)	0.647 (± 0.492)		
IVA, Week 4: Ctrough (n = 179, 174)	0.108 (± 0.112)	0.164 (± 0.207)		
IVA, Week 4: C3-6h (n = 168, 164)	0.473 (± 0.239)	0.636 (± 0.38)		
IVA, Week 8: Ctrough (n = 177, 177)	0.102 (± 0.13)	0.182 (± 0.293)		
IVA, Week 8: C3-6h (n = 170, 174)	0.513 (± 0.277)	0.71 (± 0.567)		
IVA, Week 16: Ctrough (n = 173, 171)	0.113 (± 0.218)	0.163 (± 0.237)		
M-1 IVA, Day 1: C3-6h (n = 180, 181)	2.65 (± 1.29)	2.51 (± 1.3)		
M-1 IVA, Day 15: C3-6h (n = 176, 174)	1.85 (± 0.86)	2.21 (± 1.08)		
M-1 IVA, Week 4: Ctrough (n = 179, 174)	0.501 (± 0.455)	0.676 (± 0.612)		
M-1 IVA, Week 4: C3-6h (n = 168, 164)	1.88 (± 0.953)	2.11 (± 1.12)		
M-1 IVA, Week 8: Ctrough (n = 177, 177)	0.463 (± 0.495)	0.672 (± 0.704)		
M-1 IVA, Week 8: C3-6h (n = 170, 174)	1.91 (± 0.91)	2.15 (± 1.19)		
M-1 IVA, Week 16: Ctrough (n = 173, 171)	0.465 (± 0.449)	0.643 (± 0.594)		
M-6 IVA, Day 1: C3-6h (n = 180, 181)	0.996 (± 0.797)	0.993 (± 0.82)		
M-6 IVA, Day 15: C3-6h (n = 176, 174)	2.99 (± 1.68)	3.62 (± 2.18)		
M-6 IVA, Week 4: Ctrough (n = 179, 174)	1.64 (± 1.2)	1.73 (± 1.34)		
M-6 IVA, Week 4: C3-6h (n = 168, 164)	2.64 (± 1.45)	3.07 (± 1.84)		
M-6 IVA, Week 8: Ctrough (n = 177, 177)	1.47 (± 1.17)	1.6 (± 1.22)		
M-6 IVA, Week 8: C3-6h (n = 170, 174)	2.56 (± 1.48)	3 (± 2.01)		
M-6 IVA, Week 16: Ctrough (n = 173, 171)	1.42 (± 1.05)	1.51 (± 1.29)		
LUM: Ctrough,ave (n = 182, 179)	12.7 (± 5.6)	7.81 (± 4.26)		
LUM: C3-6h,ave (n = 181, 182)	24.3 (± 7.72)	29.9 (± 9.19)		
M-28 LUM: Ctrough,ave (n = 182, 179)	1.42 (± 0.676)	1.31 (± 0.672)		
M-28 LUM: C3-6h,ave (n = 181, 182)	1.43 (± 0.64)	1.41 (± 0.62)		
IVA: Ctrough,ave (n = 182, 179)	0.11 (± 0.124)	0.17 (± 0.196)		
IVA: C3-6h,ave (n = 181, 182)	0.484 (± 0.21)	0.668 (± 0.392)		
M1-IVA: Ctrough,ave (n = 182, 179)	0.484 (± 0.391)	0.66 (± 0.504)		
M1-IVA: C3-6h,ave (n = 181, 182)	1.87 (± 0.71)	2.14 (± 0.951)		
M6-IVA: Ctrough,ave (n = 182, 179)	1.5 (± 0.897)	1.6 (± 1.08)		
M6-IVA: C3-6h,ave (n = 181, 182)	2.7 (± 1.23)	3.18 (± 1.65)		

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 non-serious AEs.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to LUM and IVA tablet q12h, up to Week 24.	
Reporting group title	LUM 600 mg qd/IVA 250 mg q12h
Reporting group description:	
LUM 600 mg plus IVA 250 mg supplied as 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
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	57 / 186 (30.65%)	51 / 186 (27.42%)	31 / 187 (16.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Hypertension			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Deep vein thrombosis			

subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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			
Medical device complication			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (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
Pyrexia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Bronchospasm			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Haemoptysis			
subjects affected / exposed	1 / 186 (0.54%)	4 / 186 (2.15%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary cavitation			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Suicidal ideation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial test positive			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Injury, poisoning and procedural complications			
Suture related complication			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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

Post procedural haematoma			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	3 / 186 (1.61%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Colitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Ileus			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Hepatitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Proteinuria			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Nephrolithiasis			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			

subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	48 / 186 (25.81%)	36 / 186 (19.35%)	24 / 187 (12.83%)
occurrences causally related to treatment / all	6 / 60	0 / 39	1 / 27
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (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
Bronchopneumonia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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 viral			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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 infection pseudomonal			

subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Influenza			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Respiratory tract infection fungal			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (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
Viraemia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (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
Viral infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 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	181 / 186 (97.31%)	179 / 186 (96.24%)	175 / 187 (93.58%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0

Hot flush			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	0	0	2
Orthostatic hypotension			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Peripheral coldness			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis limb			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 186 (11.83%)	22 / 186 (11.83%)	16 / 187 (8.56%)
occurrences (all)	27	25	20
Fatigue			
subjects affected / exposed	10 / 186 (5.38%)	13 / 186 (6.99%)	17 / 187 (9.09%)
occurrences (all)	11	14	20
Chest discomfort			
subjects affected / exposed	4 / 186 (2.15%)	4 / 186 (2.15%)	4 / 187 (2.14%)
occurrences (all)	4	4	4
Pain			

subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	5 / 187 (2.67%)
occurrences (all)	2	1	5
Malaise			
subjects affected / exposed	1 / 186 (0.54%)	4 / 186 (2.15%)	2 / 187 (1.07%)
occurrences (all)	1	6	2
Chills			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	3 / 187 (1.60%)
occurrences (all)	2	1	3
Chest pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	3 / 187 (1.60%)
occurrences (all)	1	0	3
Medical device pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	1	0	2
Influenza like illness			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	2	0	1
Thirst			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	2 / 187 (1.07%)
occurrences (all)	0	2	2
Application site pruritus			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Sensation of foreign body			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Application site rash			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Asthenia			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Device occlusion			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Energy increased			

subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Infusion site pain			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Feeling jittery			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Local swelling			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Application site irritation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Adverse drug reaction			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Application site reaction			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Discomfort			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Device leakage			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Device malfunction			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Infusion site bruising			

subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Injection site erythema			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Feeling hot			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Injection site warmth			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Medical device complication			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Injection site pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Thrombosis in device			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Vessel puncture site pain			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Drug hypersensitivity			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Food allergy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	3 / 187 (1.60%)
occurrences (all)	0	2	3
Metrorrhagia			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	4	2	1
Polymenorrhoea			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Menstruation irregular			
subjects affected / exposed	0 / 186 (0.00%)	3 / 186 (1.61%)	3 / 187 (1.60%)
occurrences (all)	0	3	4
Menorrhagia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Amenorrhoea			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Endometriosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Breast tenderness			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Uterine spasm			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Oligomenorrhoea			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			

subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Vulvovaginal pruritus			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	82 / 186 (44.09%)	69 / 186 (37.10%)	56 / 187 (29.95%)
occurrences (all)	116	89	85
Sputum increased			
subjects affected / exposed	47 / 186 (25.27%)	40 / 186 (21.51%)	29 / 187 (15.51%)
occurrences (all)	51	45	36
Dyspnoea			
subjects affected / exposed	15 / 186 (8.06%)	32 / 186 (17.20%)	31 / 187 (16.58%)
occurrences (all)	19	35	35
Nasal congestion			
subjects affected / exposed	19 / 186 (10.22%)	24 / 186 (12.90%)	13 / 187 (6.95%)
occurrences (all)	21	27	18
Haemoptysis			
subjects affected / exposed	26 / 186 (13.98%)	28 / 186 (15.05%)	20 / 187 (10.70%)
occurrences (all)	32	48	22
Oropharyngeal pain			
subjects affected / exposed	20 / 186 (10.75%)	20 / 186 (10.75%)	13 / 187 (6.95%)
occurrences (all)	23	20	13
Rhinorrhoea			
subjects affected / exposed	10 / 186 (5.38%)	11 / 186 (5.91%)	11 / 187 (5.88%)
occurrences (all)	11	12	13
Respiration abnormal			
subjects affected / exposed	13 / 186 (6.99%)	14 / 186 (7.53%)	18 / 187 (9.63%)
occurrences (all)	16	18	21
Productive cough			

subjects affected / exposed	14 / 186 (7.53%)	11 / 186 (5.91%)	5 / 187 (2.67%)
occurrences (all)	15	13	9
Sinus congestion			
subjects affected / exposed	11 / 186 (5.91%)	8 / 186 (4.30%)	8 / 187 (4.28%)
occurrences (all)	11	10	9
Wheezing			
subjects affected / exposed	9 / 186 (4.84%)	7 / 186 (3.76%)	6 / 187 (3.21%)
occurrences (all)	10	9	6
Respiratory tract congestion			
subjects affected / exposed	6 / 186 (3.23%)	8 / 186 (4.30%)	9 / 187 (4.81%)
occurrences (all)	6	10	9
Sputum discoloured			
subjects affected / exposed	6 / 186 (3.23%)	3 / 186 (1.61%)	3 / 187 (1.60%)
occurrences (all)	6	4	3
Dysphonia			
subjects affected / exposed	4 / 186 (2.15%)	3 / 186 (1.61%)	7 / 187 (3.74%)
occurrences (all)	4	3	8
Paranasal sinus hypersecretion			
subjects affected / exposed	5 / 186 (2.69%)	8 / 186 (4.30%)	6 / 187 (3.21%)
occurrences (all)	5	8	7
Rales			
subjects affected / exposed	6 / 186 (3.23%)	2 / 186 (1.08%)	2 / 187 (1.07%)
occurrences (all)	7	2	2
Asthma			
subjects affected / exposed	2 / 186 (1.08%)	4 / 186 (2.15%)	2 / 187 (1.07%)
occurrences (all)	2	6	2
Epistaxis			
subjects affected / exposed	2 / 186 (1.08%)	5 / 186 (2.69%)	1 / 187 (0.53%)
occurrences (all)	2	5	1
Upper-airway cough syndrome			
subjects affected / exposed	2 / 186 (1.08%)	2 / 186 (1.08%)	3 / 187 (1.60%)
occurrences (all)	2	2	3
Bronchial obstruction			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	2	1	2
Increased viscosity of bronchial			

secretion			
subjects affected / exposed	3 / 186 (1.61%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	4	0	0
Painful respiration			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	3 / 187 (1.60%)
occurrences (all)	1	0	4
Throat irritation			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Nasal discharge discolouration			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	2	2
Sneezing			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Pleuritic pain			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Rhinitis allergic			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	2	1	0
Bronchospasm			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Dyspnoea exertional			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Nasal polyps			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Sputum decreased			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	0	2	0

Hiccups			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Bronchial secretion retention			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Hyperventilation			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Increased bronchial secretion			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Lung disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Nasal discomfort			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Lung hyperinflation			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Pharyngeal exudate			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Pharyngeal erythema			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Pleurisy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Pharyngeal oedema			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1

Respiratory disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Respiratory gas exchange disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Sinus disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Pulmonary pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Respiratory tract irritation			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Rhonchi			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Upper respiratory tract congestion			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 186 (3.76%)	5 / 186 (2.69%)	2 / 187 (1.07%)
occurrences (all)	7	5	2
Depression			
subjects affected / exposed	3 / 186 (1.61%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	3	1	1
Anxiety			
subjects affected / exposed	2 / 186 (1.08%)	2 / 186 (1.08%)	2 / 187 (1.07%)
occurrences (all)	2	2	2
Libido decreased			

subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Mental disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Mood altered			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Sleep disorder			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Nightmare			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 186 (2.69%)	3 / 186 (1.61%)	5 / 187 (2.67%)
occurrences (all)	5	3	5
Blood creatine phosphokinase increased			
subjects affected / exposed	10 / 186 (5.38%)	4 / 186 (2.15%)	12 / 187 (6.42%)
occurrences (all)	11	4	17
Pulmonary function test decreased			
subjects affected / exposed	14 / 186 (7.53%)	5 / 186 (2.69%)	3 / 187 (1.60%)
occurrences (all)	16	5	3
Bacterial test positive			
subjects affected / exposed	1 / 186 (0.54%)	4 / 186 (2.15%)	7 / 187 (3.74%)
occurrences (all)	1	4	7
Alanine aminotransferase increased			
subjects affected / exposed	4 / 186 (2.15%)	2 / 186 (1.08%)	4 / 187 (2.14%)
occurrences (all)	4	2	4
Forced expiratory volume decreased			

subjects affected / exposed	4 / 186 (2.15%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	4	0	2
Weight decreased			
subjects affected / exposed	2 / 186 (1.08%)	3 / 186 (1.61%)	2 / 187 (1.07%)
occurrences (all)	2	3	3
Hepatic enzyme increased			
subjects affected / exposed	0 / 186 (0.00%)	4 / 186 (2.15%)	2 / 187 (1.07%)
occurrences (all)	0	4	3
Sputum abnormal			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	2	0	2
Blood glucose increased			
subjects affected / exposed	1 / 186 (0.54%)	3 / 186 (1.61%)	1 / 187 (0.53%)
occurrences (all)	1	3	1
Blood creatinine increased			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	2	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Body temperature increased			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	0	3	1
Blood glucose decreased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	3
Eosinophil count increased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Atypical mycobacterium test positive			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Fungal test positive			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Blood immunoglobulin E increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Blood iron decreased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Blood calcium increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Blood sodium decreased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Breath sounds abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Blood urine present			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Blood sodium increased			

subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Coagulation test abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Crystal urine present			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram PR shortened			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Haemophilus test positive			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	2
Liver function test abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Mean cell volume increased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Mean cell haemoglobin decreased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Oxygen saturation decreased			

subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	2
Red blood cell count decreased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Serum ferritin decreased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Vitamin D decreased			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 186 (1.08%)	3 / 186 (1.61%)	3 / 187 (1.60%)
occurrences (all)	2	3	3
Muscle strain			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	3 / 187 (1.60%)
occurrences (all)	2	1	3
Procedural pain			

subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	1	1	2
Laceration			
subjects affected / exposed	1 / 186 (0.54%)	3 / 186 (1.61%)	1 / 187 (0.53%)
occurrences (all)	1	3	1
Joint injury			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Arthropod bite			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Sunburn			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Concussion			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Alcohol poisoning			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Vaccination complication			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	2	0	1
Arthropod sting			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Animal bite			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Ankle fracture			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Iliotibial band syndrome			

subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Foreign body			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Ligament injury			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Joint dislocation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Splinter			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Stoma site irritation			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Road traffic accident			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			

subjects affected / exposed	5 / 186 (2.69%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	5	0	2
Talipes			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Tachycardia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Atrioventricular block first degree			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Sinus arrhythmia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Cyanosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Ventricular extrasystoles			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Nervous system disorders			
Sinus headache			
subjects affected / exposed	7 / 186 (3.76%)	15 / 186 (8.06%)	7 / 187 (3.74%)
occurrences (all)	8	16	11
Headache			
subjects affected / exposed	33 / 186 (17.74%)	30 / 186 (16.13%)	29 / 187 (15.51%)
occurrences (all)	37	39	36
Dizziness			

subjects affected / exposed	5 / 186 (2.69%)	7 / 186 (3.76%)	3 / 187 (1.60%)
occurrences (all)	5	7	3
Lethargy			
subjects affected / exposed	3 / 186 (1.61%)	3 / 186 (1.61%)	2 / 187 (1.07%)
occurrences (all)	3	3	2
Dysgeusia			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Migraine			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	2	1	1
Amnesia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Hypoaesthesia			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Tremor			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Paraesthesia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Intercostal neuralgia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Parosmia			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Convulsion			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Cervicogenic headache			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Ageusia			

subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Coordination abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hyperaesthesia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Epilepsy			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hypertonia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hyposmia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Nerve compression			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Muscle contractions involuntary			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Loss of consciousness			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Increased tendency to bruise			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	3	0	0
Leukopenia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Eosinophilia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	3 / 187 (1.60%)
occurrences (all)	1	1	3
Ear pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	3 / 187 (1.60%)
occurrences (all)	0	1	3
Tympanic membrane disorder			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Ear discomfort			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	1	1	1
Vertigo			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Vertigo positional			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Middle ear effusion			

subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	0	0	2
Vision blurred			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Blindness transient			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Conjunctival hyperaemia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Eye irritation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Periorbital oedema			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Visual acuity reduced			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1

Photopsia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 186 (10.22%)	15 / 186 (8.06%)	10 / 187 (5.35%)
occurrences (all)	21	24	12
Diarrhoea			
subjects affected / exposed	18 / 186 (9.68%)	20 / 186 (10.75%)	21 / 187 (11.23%)
occurrences (all)	19	28	24
Nausea			
subjects affected / exposed	17 / 186 (9.14%)	20 / 186 (10.75%)	32 / 187 (17.11%)
occurrences (all)	18	22	39
Flatulence			
subjects affected / exposed	10 / 186 (5.38%)	11 / 186 (5.91%)	13 / 187 (6.95%)
occurrences (all)	10	13	13
Abdominal pain upper			
subjects affected / exposed	8 / 186 (4.30%)	15 / 186 (8.06%)	7 / 187 (3.74%)
occurrences (all)	8	16	7
Vomiting			
subjects affected / exposed	9 / 186 (4.84%)	12 / 186 (6.45%)	9 / 187 (4.81%)
occurrences (all)	9	14	9
Abdominal distension			
subjects affected / exposed	2 / 186 (1.08%)	6 / 186 (3.23%)	5 / 187 (2.67%)
occurrences (all)	2	6	6
Constipation			
subjects affected / exposed	8 / 186 (4.30%)	5 / 186 (2.69%)	6 / 187 (3.21%)
occurrences (all)	8	5	6
Dyspepsia			
subjects affected / exposed	1 / 186 (0.54%)	3 / 186 (1.61%)	5 / 187 (2.67%)
occurrences (all)	1	3	5
Frequent bowel movements			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	7 / 187 (3.74%)
occurrences (all)	2	1	7
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	6 / 187 (3.21%)
occurrences (all)	1	1	6
Abdominal discomfort			
subjects affected / exposed	0 / 186 (0.00%)	3 / 186 (1.61%)	3 / 187 (1.60%)
occurrences (all)	0	4	3
Steatorrhoea			
subjects affected / exposed	2 / 186 (1.08%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	2	2	2
Eructation			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	1	1	3
Mouth ulceration			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Post-tussive vomiting			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Abdominal tenderness			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Abnormal faeces			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Aerophagia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Epigastric discomfort			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1

Faecaloma			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Faeces soft			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Food poisoning			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Gastritis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorder			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Gastrointestinal tract irritation			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1

Haemorrhoids			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Lip pain			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Lip ulceration			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Retching			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Odynophagia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Oesophageal pain			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Tongue discolouration			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Tongue disorder			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Tooth development disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Umbilical hernia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Tooth impacted			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1

Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Hepatic pain			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Cholecystitis acute			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 186 (2.69%)	8 / 186 (4.30%)	18 / 187 (9.63%)
occurrences (all)	5	8	19
Acne			
subjects affected / exposed	4 / 186 (2.15%)	8 / 186 (4.30%)	1 / 187 (0.53%)
occurrences (all)	4	8	1
Hyperhidrosis			
subjects affected / exposed	2 / 186 (1.08%)	5 / 186 (2.69%)	3 / 187 (1.60%)
occurrences (all)	2	5	3
Pruritus			
subjects affected / exposed	3 / 186 (1.61%)	2 / 186 (1.08%)	2 / 187 (1.07%)
occurrences (all)	3	2	2
Alopecia			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	3 / 187 (1.60%)
occurrences (all)	1	1	3
Night sweats			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	1	1	2
Urticaria			
subjects affected / exposed	2 / 186 (1.08%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	2	2	0
Eczema			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	2	2	0
Erythema			

subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Onychoclasis			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Dry skin			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Red man syndrome			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Skin odour abnormal			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Rash pruritic			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Cutaneous lupus erythematosus			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Blister			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hair texture abnormal			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Drug eruption			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Lividity			

subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Ingrowing nail			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Papule			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Pruritus allergic			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Pruritus generalised			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	1	2	1
Calculus ureteric			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0

Pollakiuria			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Proteinuria			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Haematuria			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Renal colic			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Urine odour abnormal			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Early menarche			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 186 (3.23%)	5 / 186 (2.69%)	9 / 187 (4.81%)
occurrences (all)	7	6	10
Myalgia			
subjects affected / exposed	8 / 186 (4.30%)	6 / 186 (3.23%)	3 / 187 (1.60%)
occurrences (all)	8	6	4
Arthralgia			
subjects affected / exposed	7 / 186 (3.76%)	2 / 186 (1.08%)	6 / 187 (3.21%)
occurrences (all)	8	3	6
Flank pain			

subjects affected / exposed	2 / 186 (1.08%)	3 / 186 (1.61%)	3 / 187 (1.60%)
occurrences (all)	2	4	3
Musculoskeletal chest pain			
subjects affected / exposed	1 / 186 (0.54%)	8 / 186 (4.30%)	1 / 187 (0.53%)
occurrences (all)	1	8	1
Musculoskeletal pain			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	3 / 187 (1.60%)
occurrences (all)	1	2	3
Pain in extremity			
subjects affected / exposed	2 / 186 (1.08%)	3 / 186 (1.61%)	2 / 187 (1.07%)
occurrences (all)	2	3	2
Neck pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Muscle spasms			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	2	1	0
Muscle twitching			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	0	1	2
Muscle tightness			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Tendonitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Joint swelling			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Arthropathy			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	2
Arthritis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Bone cyst			

subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Foot deformity			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hypermobility syndrome			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Chondritis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Muscle contracture			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Musculoskeletal discomfort			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Pubic pain			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Tendon pain			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Rhabdomyolysis			

subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	74 / 186 (39.78%)	58 / 186 (31.18%)	50 / 187 (26.74%)
occurrences (all)	101	77	65
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 186 (6.99%)	13 / 186 (6.99%)	10 / 187 (5.35%)
occurrences (all)	15	15	11
Nasopharyngitis			
subjects affected / exposed	20 / 186 (10.75%)	14 / 186 (7.53%)	22 / 187 (11.76%)
occurrences (all)	23	15	26
Sinusitis			
subjects affected / exposed	7 / 186 (3.76%)	17 / 186 (9.14%)	11 / 187 (5.88%)
occurrences (all)	8	19	12
Upper respiratory tract infection			
subjects affected / exposed	10 / 186 (5.38%)	8 / 186 (4.30%)	20 / 187 (10.70%)
occurrences (all)	12	9	26
Rhinitis			
subjects affected / exposed	6 / 186 (3.23%)	14 / 186 (7.53%)	8 / 187 (4.28%)
occurrences (all)	8	21	11
Pharyngitis			
subjects affected / exposed	4 / 186 (2.15%)	3 / 186 (1.61%)	3 / 187 (1.60%)
occurrences (all)	4	3	3
Influenza			
subjects affected / exposed	3 / 186 (1.61%)	6 / 186 (3.23%)	11 / 187 (5.88%)
occurrences (all)	3	6	11
Gastroenteritis			
subjects affected / exposed	5 / 186 (2.69%)	4 / 186 (2.15%)	4 / 187 (2.14%)
occurrences (all)	5	4	4
Respiratory tract infection viral			
subjects affected / exposed	1 / 186 (0.54%)	3 / 186 (1.61%)	2 / 187 (1.07%)
occurrences (all)	1	4	2
Viral infection			

subjects affected / exposed	4 / 186 (2.15%)	4 / 186 (2.15%)	0 / 187 (0.00%)
occurrences (all)	5	4	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 186 (0.00%)	5 / 186 (2.69%)	3 / 187 (1.60%)
occurrences (all)	0	6	3
Bronchitis			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	2 / 187 (1.07%)
occurrences (all)	1	2	3
Ear infection			
subjects affected / exposed	3 / 186 (1.61%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	3	1	1
Oral candidiasis			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	2 / 187 (1.07%)
occurrences (all)	1	2	2
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	3 / 187 (1.60%)
occurrences (all)	0	2	3
Gastroenteritis viral			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	2 / 187 (1.07%)
occurrences (all)	1	1	2
Respiratory tract infection			
subjects affected / exposed	2 / 186 (1.08%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	2	2	1
Urinary tract infection			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	1	2	1
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 186 (0.00%)	3 / 186 (1.61%)	1 / 187 (0.53%)
occurrences (all)	0	6	1
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 186 (1.08%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	2	1	3
Bronchopulmonary aspergillosis allergic			

subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Acute sinusitis			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	3	0	2
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Laryngitis			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	1 / 187 (0.53%)
occurrences (all)	0	2	1
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Gingivitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Clostridium difficile infection			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	2 / 187 (1.07%)
occurrences (all)	0	0	4
Conjunctivitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Oral fungal infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Oral herpes			
subjects affected / exposed	1 / 186 (0.54%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	1	1	0
Infectious mononucleosis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1
Rash pustular			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	1	0	1

Otitis externa			
subjects affected / exposed	2 / 186 (1.08%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	2	0	0
Acarodermatitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Chronic sinusitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Bacterial disease carrier			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Bronchitis viral			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Clostridium difficile colitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Device related infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Eyelid infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0

Epididymitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Gynaecological chlamydia infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Genital herpes			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Infected bites			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Infusion site infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Localised infection			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1

Lung infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Lung infection pseudomonal			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Nipple infection			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Pharyngitis bacterial			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Pseudomonas bronchitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Tinea versicolour			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Vaginitis bacterial			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0

Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	5 / 186 (2.69%)	4 / 186 (2.15%)	2 / 187 (1.07%)
occurrences (all)	5	4	2
Decreased appetite			
subjects affected / exposed	5 / 186 (2.69%)	7 / 186 (3.76%)	12 / 187 (6.42%)
occurrences (all)	5	8	13
Hyperglycaemia			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	3 / 187 (1.60%)
occurrences (all)	1	2	3
Dehydration			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	1 / 187 (0.53%)
occurrences (all)	0	1	1
Gout			
subjects affected / exposed	1 / 186 (0.54%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	1	2	0
Vitamin D deficiency			
subjects affected / exposed	0 / 186 (0.00%)	2 / 186 (1.08%)	0 / 187 (0.00%)
occurrences (all)	0	2	0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 186 (0.00%)	0 / 186 (0.00%)	1 / 187 (0.53%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	0
Vitamin A deficiency			

subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Vitamin E deficiency			
subjects affected / exposed	0 / 186 (0.00%)	1 / 186 (0.54%)	0 / 187 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	1 / 186 (0.54%)	0 / 186 (0.00%)	0 / 187 (0.00%)
occurrences (all)	1	0	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 Followup Visit was provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported