



Clinical trial results:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of VX-770 in Subjects Aged 12 Years and Older With Cystic Fibrosis who are 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	2009-010261-23
Trial protocol	Outside EU/EEA
Global end of trial date	29 May 2013

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 Re-QC per EMA guidance to verify that there are no data-related error in the document due to EudraCT system issues impacting finalized results postings

Trial information

Trial identification

Sponsor protocol code	VX08-770-104
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00953706
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000335-PIP01-08
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	27 August 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of ivacaftor in subjects with cystic fibrosis (CF) who were aged 12 years or older and were homozygous for the F508del-CF transmembrane conductance regulator (CFTR) mutation.

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	21 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	United States: 140
Worldwide total number of subjects	140
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	50
Adults (18-64 years)	90
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A 2-week run-in period was included to establish the baseline assessments on Day 1 after ensuring that subjects were properly adhering to their cystic fibrosis (CF) medication.

Period 1

Period 1 title	Part A (16-Week Double-Blind Treatment)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo – Part A

Arm description:

Placebo matched to ivacaftor tablet orally every 12 hours (q12h) for 16 weeks during Part A (double-blind treatment period).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral tablet every 12 hours (q12h) for 16 weeks.

Arm title	Ivacaftor – Part A
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Arm description:

Ivacaftor 150 milligram (mg) tablet orally q12h for 16 weeks during Part A (double-blind treatment period)

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

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor q12h for 16 weeks.

Number of subjects in period 1	Placebo – Part A	Ivacaftor – Part A
Started	28	112
Completed	26	104
Not completed	2	8
Adverse event	2	3
Noncompliance with Study Requirements	-	2
Sponsor Decision	-	1
Lost to follow-up	-	1
Required Prohibited Medication	-	1

Period 2

Period 2 title	Part B (96-Week Open-Label Extension)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Ivacaftor – Part B

Arm description:

Subjects who received placebo during Part A, received ivacaftor 150 mg tablet orally q12h for 96 weeks during Part B (open-label extension period).

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

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor q12h for 96 weeks.

Arm title	Ivacaftor/Ivacaftor – Part B
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Arm description:

Subjects who received ivacaftor during Part A, received ivacaftor 150 mg tablet orally q12h for 96 weeks during Part B (open-label extension period).

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

Dosage and administration details:

Oral tablet of 150 mg of ivacaftor q12h for 96 weeks.

Number of subjects in period 2^[1]	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B
Started	5	33
Completed	0	0
Not completed	5	33
Consent withdrawn by subject	1	2
Adverse event	-	2
Noncompliance with Study Requirements	-	1
Unspecified	-	2
Study Termination by Sponsor	4	25
Required Prohibited Medication	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: From Placebo – Part A arm only 5 subjects continued in Part B. From Ivacaftor – Part A arm only 33 subjects continued in Part B.

Baseline characteristics

Reporting groups

Reporting group title	Placebo – Part A
Reporting group description: Placebo matched to ivacaftor tablet orally every 12 hours (q12h) for 16 weeks during Part A (double-blind treatment period).	
Reporting group title	Ivacaftor – Part A
Reporting group description: Ivacaftor 150 milligram (mg) tablet orally q12h for 16 weeks during Part A (double-blind treatment period)	

Reporting group values	Placebo – Part A	Ivacaftor – Part A	Total
Number of subjects	28	112	140
Age categorical			
Units: Subjects			
12 to 17 Years	6	44	50
18 to 24 Years	10	32	42
25 to 39 Years	12	26	38
40 to 45 Years	0	5	5
> 45 Years	0	5	5
Age continuous			
Units: years			
arithmetic mean	25	22.8	
standard deviation	± 8.35	± 10.26	-
Gender categorical			
Units: Subjects			
Female	12	54	66
Male	16	58	74
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	27	110	137
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	0	1	1
White	28	111	139
Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1), Categorical			
Percent predicted for age, gender, and height.			
Units: Subjects			
< 70%	15	38	53
≥ 70% to ≤ 90%	5	35	40
> 90%	8	39	47
Weight			
Units: kilograms			
arithmetic mean	63.2	58.2	
standard deviation	± 14.96	± 13.49	-
Body Mass Index			

Units: kilogram per square meter			
arithmetic mean	22.2	21.2	
standard deviation	± 4.48	± 3.25	-
Sweat Chloride			
Units: millimoles per liter			
arithmetic mean	102.4	101.4	
standard deviation	± 7.91	± 10.28	-
ppFEV1, Continuous			
Percent predicted for age, gender, and height.			
Units: percentage			
arithmetic mean	74.8	79.7	
standard deviation	± 24.06	± 22.67	-

End points

End points reporting groups

Reporting group title	Placebo – Part A
Reporting group description: Placebo matched to ivacaftor tablet orally every 12 hours (q12h) for 16 weeks during Part A (double-blind treatment period).	
Reporting group title	Ivacaftor – Part A
Reporting group description: Ivacaftor 150 milligram (mg) tablet orally q12h for 16 weeks during Part A (double-blind treatment period)	
Reporting group title	Placebo/Ivacaftor – Part B
Reporting group description: Subjects who received placebo during Part A, received ivacaftor 150 mg tablet orally q12h for 96 weeks during Part B (open-label extension period).	
Reporting group title	Ivacaftor/Ivacaftor – Part B
Reporting group description: Subjects who received ivacaftor during Part A, received ivacaftor 150 mg tablet orally q12h for 96 weeks during Part B (open-label extension period).	

Primary: Part A : Absolute Change from Part A Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 16

End point title	Part A : Absolute Change from Part A Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) Through Week 16
End point description: Spirometry (as measured by ppFEV1) is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies. FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. ppFEV1 (predicted for age, gender, race and height) was calculated using the Knudson method. Analysis was performed on Part A Full Analysis Set (FAS) defined as all randomized subjects who received at least 1 dose of study drug during Part A. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe: Part A baseline through Week 16	

End point values	Placebo – Part A	Ivacaftor – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	111		
Units: percent predicted of FEV1				
least squares mean (standard error)	-0.2 (± 1.1)	1.5 (± 0.5)		

Statistical analyses

Statistical analysis title	Part A: ppFEV1 Through Week 16
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Statistical analysis description:

The primary analysis for the primary efficacy variable was based on a Mixed-Effects Model for Repeated Measures (MMRM). The model included absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) as the dependent variable, treatment (ivacaftor versus placebo) and visit as fixed effects, and subject as a random effect, with adjustment for age and continuous baseline value of percent predicted FEV1.

Comparison groups	Placebo – Part A v Ivacaftor – Part A
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1509
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	4.1
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: Part A: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score Through Week 16 (Respiratory Domain Score, Pooled)

End point title	Part A: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score Through Week 16 (Respiratory Domain Score, Pooled)
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End point description:

The CFQR 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), score range: 0-100; Higher scores indicating fewer symptoms and better health-related quality of life. Analysis was performed on Part A FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

baseline through 16 weeks

End point values	Placebo – Part A	Ivacaftor – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	111		
Units: score on a scale				
least squares mean (standard error)	-1.4 (± 1.9)	-0.1 (± 1)		

Statistical analyses

Statistical analysis title	Part A: CFQ-R Score Through Week 16
Statistical analysis description:	
Analysis for the respiratory domain score endpoint was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from Mixed-Effects Model for Repeated Measures (MMRM) with the dependent variable being absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for for age and baseline value for CFQ-R score, using unstructured covariance matrix .	
Comparison groups	Placebo – Part A v Ivacaftor – Part A
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5408
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	5.6
Variability estimate	Standard error of the mean
Dispersion value	2.1

Secondary: Part A: Absolute Change From Baseline in Sweat Chloride Concentration Through Week 16

End point title	Part A: Absolute Change From Baseline in Sweat Chloride Concentration Through Week 16
End point description:	
The sweat chloride (quantitative pilocarpine iontophoresis) test is a standard diagnostic tool for cystic fibrosis (CF), serving as an indicator of cystic fibrosis transmembrane conductance regulator (CFTR) activity. Analysis was performed on Part A FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
baseline through 16 weeks	

End point values	Placebo – Part A	Ivacaftor – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	111		
Units: millimoles per liter				
least squares mean (standard error)	0.1 (± 1.2)	-2.7 (± 0.6)		

Statistical analyses

Statistical analysis title	Part A: Sweat Chloride Through Week 16
Statistical analysis description:	
Analysis for this variable was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from Mixed-Effects Model for Repeated Measures (MMRM) with dependent variable being absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for continuous age and baseline value for age, sweat chloride, using unstructured covariance matrix.	
Comparison groups	Placebo – Part A v Ivacaftor – Part A
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0384
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	1.4

Secondary: Part A: Rate of Change From Baseline in Weight Through Week 16

End point title	Part A: Rate of Change From Baseline in Weight Through Week 16
End point description:	
As malnutrition is common in subjects with cystic fibrosis (CF) because of increased energy expenditures due to lung disease and fat malabsorption, body weight is an important clinical measure of nutritional status. Analysis was performed on Part A FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
baseline to 16 weeks	

End point values	Placebo – Part A	Ivacaftor – Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	112		
Units: kilograms per 112 days				
least squares mean (standard error)	0.9 (± 0.4)	0.8 (± 0.2)		

Statistical analyses

Statistical analysis title	Part A: Weight Through Week 16
Statistical analysis description:	
The analysis used the linear mixed model with treatment as fixed effects, visit (days on study) and	

treatment by visit interaction as random effects, with adjustment for age group (< 18 years and ≥ 18 years) and percent predicted forced expiratory volume (FEV1) severity (< 70%, ≥ 70% to ≤ 90%, > 90%) at screening, with random intercept and random slope. Rate of change in the study period is the slope of weight versus time (days) multiplied by the number of days in the study period (112 days).

Comparison groups	Placebo – Part A v Ivacaftor – Part A
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7265
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.5

Secondary: Part B : Absolute Change From Part A and Part B Baseline in ppFEV1 Through Week 64

End point title	Part B : Absolute Change From Part A and Part B Baseline in ppFEV1 Through Week 64
End point description:	ppFEV1 is defined in primary endpoint. Analysis was performed on Part B FAS defined as all subjects who received at least 1 dose of study drug during Part B. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.
End point type	Secondary
End point timeframe:	Change from Part A baseline: Part A Baseline, Week 64; Change from Part B baseline: Part B Baseline (Week 16), Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	27		
Units: percent predicted of FEV1				
arithmetic mean (standard deviation)				
Change From Part A Baseline at Week 64	8.9398 (± 9.703)	2.7233 (± 10.52046)		
Change From Part B Baseline at Week 64	3.5593 (± 7.95875)	-5.0565 (± 11.44783)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Rate of Decline From Part A Baseline in ppFEV1 Through Week 64

End point title	Part B : Rate of Decline From Part A Baseline in ppFEV1 Through Week 64
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End point description:

ppFEV1 is defined in primary endpoint. Analysis was performed on Part B FAS.

End point type	Secondary
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End point timeframe:

Part A baseline through Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	33		
Units: percent predicted of FEV1 per 448 days				
least squares mean (standard error)	5.7445 (± 3.681)	-1.0738 (± 1.5025)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Rate of Decline From Part B Baseline in ppFEV1 Through Week 64

End point title	Part B : Rate of Decline From Part B Baseline in ppFEV1 Through Week 64
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End point description:

ppFEV1 is defined in primary endpoint. Analysis was performed on Part B FAS.

End point type	Secondary
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End point timeframe:

Part B baseline through Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	33		
Units: percent predicted of FEV1 per 336 days				
least squares mean (standard error)	5.3409 (± 4.579)	-5.2994 (± 1.8871)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Absolute Change From Part A and Part B Baseline in CFQ-R Respiratory Domain Score Through Week 64

End point title	Part B : Absolute Change From Part A and Part B Baseline in CFQ-R Respiratory Domain Score Through Week 64
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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), score range: 0-100; Higher scores indicating fewer symptoms and better health-related quality of life. Analysis was performed on Part B FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Change from Part A baseline: Part A Baseline, Week 64; Change from Part B baseline: Part B Baseline (Week 16), Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	26		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change From Part A Baseline at Week 64	2.1 (± 11.443)	1.5 (± 15.778)		
Change From Part B Baseline at Week 64	2.08 (± 17.763)	2.62 (± 15.899)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Absolute Change from Part A and Part B Baseline in Sweat Chloride Concentration Through Week 64

End point title	Part B : Absolute Change from Part A and Part B Baseline in Sweat Chloride Concentration Through Week 64
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End point description:

The sweat chloride (quantitative pilocarpine iontophoresis) test is a standard diagnostic tool for CF, serving as an indicator of CFTR activity. Analysis was performed on Part B FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Change from Part A baseline: Part A Baseline, Week 64; Change from Part B baseline: Part B Baseline (Week 16), Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	26		
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Change From Part A Baseline at Week 64	-7.13 (± 15.612)	-3.65 (± 11.963)		
Change From Part B Baseline at Week 64	-3.88 (± 7.685)	-2.44 (± 11.037)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Absolute Change From Part A and Part B Baseline in Weight Through Week 64

End point title	Part B : Absolute Change From Part A and Part B Baseline in Weight Through Week 64
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End point description:

As malnutrition is common in subjects with CF because of increased energy expenditures due to lung disease and fat malabsorption, body weight is an important clinical measure of nutritional status. Analysis was performed on Part B FAS. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Change from Part A baseline: Part A Baseline, Week 64; Change from Part B baseline: Part B Baseline (Week 16), Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	27		
Units: kilograms (kg)				
arithmetic mean (standard deviation)				
Change From Part A Baseline at Week 64	3 (± 3.55)	2.35 (± 5.6)		
Change From Part B Baseline at Week 64	1.28 (± 2.243)	1.45 (± 3.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Number of Subjects With Pulmonary Exacerbations

End point title	Part B : Number of Subjects With Pulmonary Exacerbations
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End point description:

Pulmonary exacerbation was defined as new, or changed, antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs/symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38 degrees Celsius; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent (%); and radiographic changes indicative of pulmonary infection. Analysis was performed on Part B FAS.

End point type	Secondary
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End point timeframe:

Part B baseline through Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	33		
Units: subjects				
number (not applicable)	4	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Number of Pulmonary Exacerbation Events

End point title	Part B : Number of Pulmonary Exacerbation Events
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End point description:

Pulmonary exacerbation was defined as new, or changed, antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs/symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38 degrees Celsius; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 %; and radiographic changes indicative of pulmonary infection. Analysis was performed on Part B FAS.

End point type	Secondary
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End point timeframe:

Part B baseline through Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	33		
Units: events				
number (not applicable)	6	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B : Number of Pulmonary Exacerbation Events per Subject per Year

End point title	Part B : Number of Pulmonary Exacerbation Events per Subject per Year
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End point description:

Pulmonary exacerbation was defined as new, or changed, antibiotic therapy (intravenous, inhaled, or oral) for any 4 or more of the following signs/symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38 degrees Celsius; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 %; and radiographic changes indicative of pulmonary infection. Analysis was performed on Part B FAS.

End point type	Secondary
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End point timeframe:

Part B baseline through Week 64

End point values	Placebo/Ivacaftor – Part B	Ivacaftor/Ivacaftor – Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	33		
Units: events per subject per year				
number (not applicable)	1.1	0.82		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (serious and non-serious) were collected from signing of informed consent through 2 years after last dose (in Part B) of study drug (median treatment duration: 112 days for Part A and 381 days for Part B)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Part A: Placebo
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Reporting group description:

Oral tablet q12h for 16 weeks.

Reporting group title	Part A: 150 mg Ivacaftor q12h
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Reporting group description:

Oral tablet of 150 mg of ivacaftor q12h for 16 weeks.

Reporting group title	Part B: Placebo/Ivacaftor
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Reporting group description:

Oral tablet of 150 mg of ivacaftor q12h for up to 76 weeks in subjects who received placebo in Part A.

Reporting group title	Part B : Ivacaftor/Ivacaftor
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Reporting group description:

Oral tablet of 150 mg of ivacaftor q12h for up to 76 weeks in subjects who received Ivacaftor in Part A.

Serious adverse events	Part A: Placebo	Part A: 150 mg Ivacaftor q12h	Part B: Placebo/Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 28 (21.43%)	15 / 112 (13.39%)	2 / 5 (40.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Brain Injury			

subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	5 / 28 (17.86%)	10 / 112 (8.93%)	2 / 5 (40.00%)
occurrences causally related to treatment / all	0 / 6	2 / 12	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (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
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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			
Haemoptysis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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
Hypoxia			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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
Nasal polyps			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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			
Depression			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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
Suicidal ideation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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
Anxiety			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (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
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (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
Central Line Infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B : Ivacaftor/Ivacaftor		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 33 (42.42%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic Brain Injury			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	13 / 33 (39.39%)		
occurrences causally related to treatment / all	0 / 20		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cognitive disorder			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal polyps			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Central Line Infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A: Placebo	Part A: 150 mg Ivacaftor q12h	Part B: Placebo/Ivacaftor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 28 (89.29%)	98 / 112 (87.50%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Focal nodular hyperplasia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Skin papilloma subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Surgical and medical procedures Wisdom teeth removal subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	8 / 112 (7.14%) 8	0 / 5 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	9 / 112 (8.04%) 10	0 / 5 (0.00%) 0
Catheter site pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	2 / 112 (1.79%) 2	0 / 5 (0.00%) 0
Chills subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Application site pruritus subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 2	0 / 5 (0.00%) 0
Application site rash subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Asthenia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0

Chest pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Generalised oedema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Thirst			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Catheter related complication			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infusion site pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysmenorrhoea			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Prostatic cyst			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Testicular pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Testicular swelling			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 28 (14.29%)	34 / 112 (30.36%)	0 / 5 (0.00%)
occurrences (all)	5	43	0
Nasal congestion			
subjects affected / exposed	2 / 28 (7.14%)	13 / 112 (11.61%)	0 / 5 (0.00%)
occurrences (all)	2	14	0
Oropharyngeal pain			
subjects affected / exposed	3 / 28 (10.71%)	10 / 112 (8.93%)	0 / 5 (0.00%)
occurrences (all)	3	12	0
Productive cough			
subjects affected / exposed	1 / 28 (3.57%)	9 / 112 (8.04%)	0 / 5 (0.00%)
occurrences (all)	1	9	0
Haemoptysis			

subjects affected / exposed	1 / 28 (3.57%)	5 / 112 (4.46%)	2 / 5 (40.00%)
occurrences (all)	1	10	3
Rhinorrhea			
subjects affected / exposed	2 / 28 (7.14%)	4 / 112 (3.57%)	0 / 5 (0.00%)
occurrences (all)	2	5	0
Dyspnoea			
subjects affected / exposed	0 / 28 (0.00%)	5 / 112 (4.46%)	1 / 5 (20.00%)
occurrences (all)	0	5	1
Nasal polyps			
subjects affected / exposed	1 / 28 (3.57%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Rales			
subjects affected / exposed	1 / 28 (3.57%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Respiratory tract congestion			
subjects affected / exposed	1 / 28 (3.57%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Nasal mucosal disorder			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Pharyngeal erythema			
subjects affected / exposed	1 / 28 (3.57%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Sinus congestion			
subjects affected / exposed	1 / 28 (3.57%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Wheezing			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Asthma			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Epistaxis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pleuritic pain			

subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Respiration abnormal			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Bronchospasm			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nasal oedema			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Paranasal sinus Hypersecretion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pharyngeal disorder			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Postnasal Drip			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sputum discoloured			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Tachypnoea			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Dysphonia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	1 / 5 (20.00%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	1 / 112 (0.89%) 1	1 / 5 (20.00%) 1
Abnormal dreams subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Hallucination subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Adjustment disorder subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Investigations			
C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	6 / 112 (5.36%) 6	0 / 5 (0.00%) 0
Blood glucose increased subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	5 / 112 (4.46%) 5	0 / 5 (0.00%) 0
Pulmonary function test decreased subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	3 / 112 (2.68%) 4	0 / 5 (0.00%) 0
Bacteria Sputum Identified subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	3 / 112 (2.68%) 4	0 / 5 (0.00%) 0
Prothrombin time prolonged			

subjects affected / exposed	1 / 28 (3.57%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 28 (7.14%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 28 (7.14%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Glucose urine present			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Blood immunoglobulin G increased			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Breath sounds abnormal			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Vitamin D decreased			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
White blood cell count increased			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Antibiotic level above therapeutic			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Bacterial Culture positive			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood glucose decreased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Bone density decreased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Liver function test abnormal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sputum culture positive			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Sputum abnormal subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 112 (1.79%) 3	0 / 5 (0.00%) 0
Skin laceration subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 112 (1.79%) 2	0 / 5 (0.00%) 0
Foreign body trauma subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Joint sprain subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Muscle strain subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Procedural pain			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Procedural site reaction			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Traumatic brain injury			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Animal bite			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Arthropod sting			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Head injury			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Cystic fibrosis lung			

subjects affected / exposed	7 / 28 (25.00%)	19 / 112 (16.96%)	3 / 5 (60.00%)
occurrences (all)	8	24	6
Cystic fibrosis related diabetes			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 28 (7.14%)	11 / 112 (9.82%)	0 / 5 (0.00%)
occurrences (all)	3	17	0
Dizziness			
subjects affected / exposed	2 / 28 (7.14%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Sinus headache			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Burning sensation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hyperaesthesia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Presyncope			

subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Lymphadenopathy			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Lacrimation increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eyelid oedema			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Erythema of eyelid			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	10 / 112 (8.93%)	0 / 5 (0.00%)
occurrences (all)	1	11	0
Abdominal pain upper			
subjects affected / exposed	1 / 28 (3.57%)	7 / 112 (6.25%)	0 / 5 (0.00%)
occurrences (all)	4	8	0
Diarrhoea			
subjects affected / exposed	2 / 28 (7.14%)	6 / 112 (5.36%)	0 / 5 (0.00%)
occurrences (all)	2	7	0
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)	4 / 112 (3.57%)	3 / 5 (60.00%)
occurrences (all)	1	5	3
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	4 / 112 (3.57%)	0 / 5 (0.00%)
occurrences (all)	0	4	0
Flatulence			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Abdominal discomfort			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Aphthous stomatitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Constipation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Dental caries			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Distal ileal obstruction syndrome			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hiatus hernia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pancreatic duct dilatation			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Peptic ulcer			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Regurgitation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tooth impacted			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sensitivity of teeth			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hepatosplenomegaly			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 28 (0.00%)	9 / 112 (8.04%)	0 / 5 (0.00%)
occurrences (all)	0	9	0
Dermatitis contact			
subjects affected / exposed	0 / 28 (0.00%)	6 / 112 (5.36%)	0 / 5 (0.00%)
occurrences (all)	0	9	0
Pruritus			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Rash papular			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Rash vesicular			

subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 112 (1.79%) 3	0 / 5 (0.00%) 0
Blister subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 112 (0.00%) 0	0 / 5 (0.00%) 0
Photodermatitis subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Photosensitivity reaction subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Rash macular subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 2	0 / 5 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Red man syndrome subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 112 (0.00%) 0	1 / 5 (20.00%) 1
Renal and urinary disorders Calculus bladder subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Chromaturia subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	1 / 112 (0.89%) 1	0 / 5 (0.00%) 0

Nephrolithiasis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Renal cyst			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal failure acute			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	2 / 28 (7.14%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Arthralgia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Back pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Pain in extremity			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Joint swelling			
subjects affected / exposed	0 / 28 (0.00%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Arthritis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Bone pain			

subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Clubbing			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Myopathy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Arthropathy			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Synovial cyst			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)	11 / 112 (9.82%)	1 / 5 (20.00%)
occurrences (all)	2	13	1
Sinusitis			
subjects affected / exposed	1 / 28 (3.57%)	8 / 112 (7.14%)	1 / 5 (20.00%)
occurrences (all)	1	9	1
Rhinitis			
subjects affected / exposed	0 / 28 (0.00%)	5 / 112 (4.46%)	0 / 5 (0.00%)
occurrences (all)	0	5	0

Nasopharyngitis			
subjects affected / exposed	0 / 28 (0.00%)	4 / 112 (3.57%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Ear infection			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Laryngitis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 28 (3.57%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Acute sinusitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Candidiasis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Folliculitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Kidney infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Oral herpes			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Orchitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory moniliasis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Stenotrophomonas infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tinea infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Viral upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Bacterial disease carrier			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Body tinea			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Helicobacter gastritis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infectious mononucleosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Otitis externa			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vaginitis bacterial			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 112 (1.79%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 112 (2.68%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Gout			
subjects affected / exposed	0 / 28 (0.00%)	1 / 112 (0.89%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Glucose tolerance impaired			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypovitaminosis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 112 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B : Ivacaftor/Ivacaftor		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 33 (90.91%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Focal nodular hyperplasia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Skin papilloma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Wisdom teeth removal			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Catheter site pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Chills			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Application site pruritus			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Application site rash			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Feeling abnormal			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Influenza like illness			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Thirst			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Vessel puncture site pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Catheter related complication			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infusion site pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypersensitivity			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Dysmenorrhoea			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Prostatic cyst			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Testicular pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Testicular swelling			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 33 (45.45%)		
occurrences (all)	17		
Nasal congestion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Haemoptysis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Rhinorrhea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nasal polyps			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Rales			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Respiratory tract congestion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nasal mucosal disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pharyngeal erythema			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pleuritic pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiration abnormal			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Increased viscosity of bronchial			

secretion			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Nasal oedema			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Paranasal sinus Hypersecretion			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Pharyngeal disorder			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Postnasal Drip			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Sputum discoloured			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Tachypnoea			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Throat irritation			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Upper respiratory tract congestion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Abnormal dreams			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Hallucination			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Adjustment disorder			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pulmonary function test decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Bacteria Sputum Identified			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Glucose urine present			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood immunoglobulin G increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Breath sounds abnormal			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Forced expiratory volume decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Vitamin D decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
White blood cell count increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Antibiotic level above therapeutic			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Bacterial Culture positive			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood glucose decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Bone density decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Liver function test abnormal			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Sputum culture positive			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
International normalised ratio increased			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Oxygen saturation decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Sputum abnormal			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Foreign body trauma			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Joint injury			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Joint sprain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Procedural site reaction			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Traumatic brain injury			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Animal bite			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Arthropod sting			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Excoriation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Road traffic accident			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	11 / 33 (33.33%)		
occurrences (all)	17		
Cystic fibrosis related diabetes			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Sinus headache			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Burning sensation			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Hyperaesthesia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Migraine			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Somnolence			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Conjunctivitis allergic			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Eye pruritus			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Visual impairment			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Erythema of eyelid			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Abdominal discomfort			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Aphthous stomatitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Ascites			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		

Dental caries			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Distal ileal obstruction syndrome			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Frequent bowel movements			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hiatus hernia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pancreatic duct dilatation			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Peptic ulcer			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Regurgitation			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Tooth impacted			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Sensitivity of teeth			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Hepatosplenomegaly			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Rash papular			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Rash vesicular			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Blister			

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Photodermatosis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Red man syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Chromaturia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Nephrolithiasis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

Proteinuria			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Renal cyst			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Renal failure acute			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Urinary retention			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Joint swelling			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Clubbing			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Myopathy			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Arthropathy			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Synovial cyst			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Rhinitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		

Ear infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Oral candidiasis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Acute sinusitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Candidiasis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Clostridium difficile colitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Kidney infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		

Orchitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Pneumonia staphylococcal			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Respiratory moniliasis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Stenotrophomonas infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Tinea infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Tooth abscess			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3		
Bronchitis subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4		
Bacterial disease carrier subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Body tinea subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Cystitis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Helicobacter gastritis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0		
Infectious mononucleosis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Otitis externa subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Vaginitis bacterial subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Metabolism and nutrition disorders Hyperglycaemia			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Gout			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Glucose tolerance impaired			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypovitaminosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2009	Timing of multiple pharmacokinetic (PK) assessments and postdose standard digital electrocardiograms (ECGs) were changed. Follow-up criteria were clarified.
09 October 2009	An open-label extension period (Part B) was added. Inclusion/exclusion criteria were updated.
08 April 2010	Mandatory liver function tests were added.
02 July 2010	Subject removal criteria were updated.
10 September 2010	Clarification on SAEs collection was added.
27 October 2010	Frequency of liver function testing in Part B beyond Week 40 was adjusted.
06 June 2011	Extension Period Long-term Follow-up was added to Part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

In Part B, the treatment duration was 96 weeks; however, due to early study termination all analysis were performed up to Week 64, as planned.

Notes: