



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 | <ul style="list-style-type: none">• 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 |
|-----------------------|--------------|

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 |
|------------------|--------------------|

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 |
|------------------|------------------------------|

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 |
|----------------------------|--------------------------------|

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) |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 12.0 |

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Part A: Placebo |
|-----------------------|-----------------|

Reporting group description:

Oral tablet q12h for 16 weeks.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Part A: 150 mg Ivacaftor q12h |
|-----------------------|-------------------------------|

Reporting group description:

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

| | |
|-----------------------|---------------------------|
| Reporting group title | Part B: Placebo/Ivacaftor |
|-----------------------|---------------------------|

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 |
|-----------------------|------------------------------|

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 | | | |

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| 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 | | | |

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

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|-----------------------------|----------------|------------------|----------------|
| 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 |

| | | | |
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| 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 | | | |

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

| | | | |
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| 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 | 2 / 33 (6.06%) | | |
| occurrences (all) | 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 | | | |

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

| | | | |
|-----------------------------|----------------|--|--|
| 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: