



Clinical trial results:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of VX 770 in Subjects with Cystic Fibrosis and the G551D Mutation

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2008-007416-15 |
| Trial protocol | IE GB DE CZ FR |
| Global end of trial date | 29 November 2012 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2016 |
| First version publication date | 07 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX08-770-102 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00909532 |
| 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, +1 617-444-6777, medicalinfo@vrtx.com |
| Scientific contact | Medical Monitor, Vertex, +1 617-444-6777, 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 | 15 March 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 November 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of VX-770 after 24 weeks of treatment in subjects with cystic fibrosis (CF) with G551D cystic fibrosis 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 | 10 June 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 Kingdom: 9 |
| Country: Number of subjects enrolled | Czech Republic: 4 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Ireland: 14 |
| Country: Number of subjects enrolled | Australia: 19 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | United States: 91 |
| Worldwide total number of subjects | 161 |
| EEA total number of subjects | 42 |

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) | 36 |
| Adults (18-64 years) | 125 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study started on 10 June 2009 (signing of first informed consent). After obtaining consent and assent (where applicable), screening evaluations were completed during a period of 2 to 5 weeks (Day -35 to Day -15) before the first dose of study drug.

Pre-assignment

Screening details:

A total of 167 subjects were randomized; 161 subjects received at least 1 dose of the study drug. A 2-week run-in period was included to establish the baseline assessments on Day 1 after ensuring that subjects were properly taking their cystic fibrosis (CF) medication regimens.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks.

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

Dosage and administration details:

Placebo-matched-to-ivacaftor tablet orally q12h up to 48 weeks.

| | |
|------------------|-----------------------|
| Arm title | 150 mg Ivacaftor q12h |
|------------------|-----------------------|

Arm description:

Ivacaftor 150 mg tablet orally q12h for up to 48 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ivacaftor |
| Investigational medicinal product code | VX770 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ivacaftor 150 mg tablet administered orally q12h for up to 48 weeks.

| Number of subjects in period 1 | Placebo | 150 mg Ivacaftor q12h |
|--|---------|--------------------------|
| Started | 78 | 83 |
| Completed Treatment Period, Week 24 | 71 | 80 |
| Completed | 68 | 77 |
| Not completed | 10 | 6 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | 1 | 1 |
| 'Wrong Genotype ' | 1 | - |
| Pregnancy | - | 1 |
| Adverse event | 4 | 1 |
| 'Increased Lab Draws, Difficult Lab Stick ' | 1 | - |
| Noncompliance with Study Requirements | - | 2 |
| Prohibited Medication | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|--|-----------------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks. | |
| Reporting group title | 150 mg Ivacaftor q12h |
| Reporting group description: Ivacaftor 150 mg tablet orally q12h for up to 48 weeks. | |

| Reporting group values | Placebo | 150 mg Ivacaftor q12h | Total |
|--|---------|-----------------------|-------|
| Number of subjects | 78 | 83 | 161 |
| Age categorical Units: Subjects | | | |
| <=18 years | 17 | 19 | 36 |
| Between 18 and 65 years | 61 | 64 | 125 |
| >=65 years | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 24.7 | 26.2 | - |
| standard deviation | ± 9.21 | ± 9.85 | - |
| Gender categorical Units: Subjects | | | |
| Female | 40 | 44 | 84 |
| Male | 38 | 39 | 77 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 77 | 81 | 158 |
| Unknown or Not Reported | 1 | 2 | 3 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 77 | 81 | 158 |
| Not Allowed to Ask Per Local Regulations | 1 | 2 | 3 |
| Region of Enrollment Units: Subjects | | | |
| North America | 50 | 50 | 100 |
| Europe | 19 | 23 | 42 |
| Australia | 9 | 10 | 19 |
| Percent Predicted FEV1, Categorical Units: Subjects | | | |
| < 70% predicted FEV1 | 45 | 49 | 94 |
| ≥ 70% predicted FEV1 | 33 | 34 | 67 |
| Percent Predicted Forced Expiratory Volume in 1 Second (FEV1), Continuous [1] Units: percentage | | | |
| arithmetic mean | 63.7 | 63.5 | |

| | | | |
|--|---------|---------|---|
| standard deviation | ± 16.83 | ± 16.14 | - |
| Weight | | | |
| Units: kilograms | | | |
| arithmetic mean | 61.2 | 61.7 | |
| standard deviation | ± 13.93 | ± 14.26 | - |
| Body Mass Index | | | |
| Units: kilograms per square meter | | | |
| arithmetic mean | 21.9 | 21.7 | |
| standard deviation | ± 3.49 | ± 3.65 | - |
| Sweat Chloride | | | |
| Units: millimoles per liter (mmol/liter) | | | |
| arithmetic mean | 100.1 | 100.4 | |
| standard deviation | ± 10.63 | ± 10 | - |

End points

End points reporting groups

| | |
|--|-----------------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks. | |
| Reporting group title | 150 mg Ivacaftor q12h |
| Reporting group description: Ivacaftor 150 mg tablet orally q12h for up to 48 weeks. | |

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

| | |
|--|---|
| End point title | Absolute Mean Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24 |
| End point description: Spirometry (as measured by FEV1) is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies. Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame. | |
| End point type | Primary |
| End point timeframe: Baseline through 24 weeks | |

| End point values | Placebo | 150 mg Ivacaftor q12h | | |
|--|-----------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 83 | | |
| Units: percent of predicted volume (L) | | | | |
| least squares mean (standard error) | -0.2 (± 0.7) | 10.4 (± 0.7) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Percent Predicted FEV1 Through Week 24 |
| 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 (Day 15, Week 8, Week 16, and Week 24) as fixed effects, and subject as a random effect, with adjustment for the continuous baseline values of age and percent predicted FEV1. | |
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.6 |
| upper limit | 12.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1 |

Notes:

[1] - The primary and key secondary endpoints were analyzed using Hochberg's step-up procedure: test 1, primary ($\alpha=0.05$); test 2, CFQ-R resp domain (Wk24) and sweat chloride (Wk24)($\alpha=0.05$).

Secondary: Absolute Mean Change From Baseline in Percent Predicted FEV1 Through Week 48

| | |
|-----------------|--|
| End point title | Absolute Mean Change From Baseline in Percent Predicted FEV1 Through Week 48 |
|-----------------|--|

End point description:

Spirometry (as measured by FEV1) is a standardized assessment to evaluate lung function that is the most widely used endpoint in cystic fibrosis studies.

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

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

End point timeframe:

Baseline through 48 weeks

| End point values | Placebo | 150 mg Ivacaftor q12h | | |
|--|-------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 83 | | |
| Units: percent of predicted volume (L) | | | | |
| least squares mean (standard error) | -0.4 (\pm 0.7) | 10.1 (\pm 0.7) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Percent Predicted FEV1 Through Week 48 |
|----------------------------|--|

Statistical analysis description:

Analysis of this variable was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were obtained from Mixed-Effects Model for Repeated Measures (MMRM) with dependent variable absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for the continuous baseline values of age and percent predicted forced expiratory volume in 1 second (FEV1), using unstructured covariance matrix.

| | |
|-------------------|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
|-------------------|---------------------------------|

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.5 |
| upper limit | 12.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1 |

Notes:

[2] - There was no adjustment for multiple comparisons. Denominator degrees of freedom were estimated using the Kenward-Roger approximation. No imputation of missing data was done.

Secondary: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score Through Week 24 and Week 48 (Respiratory Domain Score, Pooled)

| | |
|-----------------|---|
| End point title | Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Score Through Week 24 and Week 48 (Respiratory Domain Score, Pooled) |
|-----------------|---|

End point description:

The CFQ-R is a health-related quality of life measure for subjects with cystic fibrosis. Each domain is scored from 0 (worst) to 100 (best). A difference of at least 4 points in the respiratory domain score of the CFQ-R is considered a minimal clinically important difference (MCID).

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

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

End point timeframe:

Baseline through 24 weeks and 48 weeks

| End point values | Placebo | 150 mg Ivacaftor q12h | | |
|--------------------------------------|-----------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 | 80 | | |
| Units: score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Change from Baseline Through Week 24 | -2.1 (± 1.3) | 6 (± 1.2) | | |
| Change from Baseline Through Week 48 | -2.7 (± 1.2) | 6 (± 1.1) | | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | CFQ-R Score Through Week 24 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Through Week 24: 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 dependent variable absolute change from baseline, fixed effects for categorical

visit and treatment group, and adjustment for continuous baseline value for age, domain score, and percent predicted FEV1, using unstructured covariance matrix.

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[3] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.7 |
| upper limit | 11.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.7 |

Notes:

[3] - Analyzed in sequence: test 1, primary ($\alpha=0.05$); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) ($\alpha=0.05$).

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | CFQ-R Score Through Week 48 |
|-----------------------------------|-----------------------------|

Statistical analysis description:

Through Week 48: Analysis for the CFQ-R respiratory domain score endpoint was similar to that of the primary analysis of the primary efficacy endpoint. Estimates were from MMRM with dependent variable absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for continuous baseline value for age, sweat chloride, and percent predicted FEV1, using unstructured covariance matrix

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 151 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[4] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.3 |
| upper limit | 11.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.7 |

Notes:

[4] - There was no adjustment for multiple comparisons.

Secondary: Absolute Change From Baseline in Sweat Chloride Concentration Through Week 24 and Week 48

| | |
|-----------------|---|
| End point title | Absolute Change From Baseline in Sweat Chloride Concentration Through Week 24 and Week 48 |
|-----------------|---|

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 population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline through 24 weeks and 48 weeks | |

| End point values | Placebo | 150 mg Ivacaftor q12h | | |
|--------------------------------------|-----------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 | 78 | | |
| Units: millimoles per liter | | | | |
| least squares mean (standard error) | | | | |
| Change from Baseline Through Week 24 | -0.8 (± 1.3) | -48.7 (± 1.2) | | |
| Change from Baseline Through Week 48 | -0.6 (± 1.3) | -48.7 (± 1.2) | | |

Statistical analyses

| Statistical analysis title | Sweat Chloride Concentration Through Week 24 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Through Week 24: 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 absolute change from baseline, fixed effects for categorical visit and treatment group, and adjustment for continuous baseline value for age, sweat chloride, and percent predicted FEV1, using unstructured covariance matrix.

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[5] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -47.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -51.3 |
| upper limit | -44.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.7 |

Notes:

[5] - Analyzed in sequence: test 1, primary ($\alpha=0.05$); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) ($\alpha=0.05$); test 3 using Hochberg's on time to pulmonary exacerbation (Wk 48) and weight (Wk 48).

| Statistical analysis title | Sweat Chloride Concentration Through Week 48 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Through Week 48: 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 absolute change from baseline, fixed effects for categorical visit and treatment

group, and adjustment for continuous baseline value for age, sweat chloride, and percent predicted FEV1, using unstructured covariance matrix.

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[6] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -48.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -51.5 |
| upper limit | -44.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.7 |

Notes:

[6] - There was no adjustment for multiple comparisons.

Secondary: Time-to-first Pulmonary Exacerbation Through Week 24 and Week 48

| | |
|-----------------|--|
| End point title | Time-to-first Pulmonary Exacerbation Through Week 24 and Week 48 |
|-----------------|--|

End point description:

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

Analysis population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

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

End point timeframe:

Baseline through 24 weeks and 48 weeks

| End point values | Placebo | 150 mg Ivacaftor q12h | | |
|--|---------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 83 | | |
| Units: proportion of event-free participants | | | | |
| number (confidence interval 95%) | | | | |
| 0 to 15 Days | 0.97 (0.9 to 0.99) | 0.98 (0.91 to 0.99) | | |
| 16 to 56 Days | 0.87 (0.77 to 0.93) | 0.89 (0.8 to 0.94) | | |
| 57 to 112 Days | 0.72 (0.61 to 0.81) | 0.83 (0.73 to 0.9) | | |
| 113 to 168 Days | 0.53 (0.41 to 0.64) | 0.78 (0.68 to 0.86) | | |
| 169 to 224 Days | 0.51 (0.39 to 0.61) | 0.75 (0.64 to 0.83) | | |

| | | | | |
|-----------------|---------------------|---------------------|--|--|
| 225 to 280 Days | 0.44 (0.32 to 0.55) | 0.7 (0.58 to 0.78) | | |
| 281 to 336 Days | 0.41 (0.29 to 0.52) | 0.67 (0.55 to 0.76) | | |

Statistical analyses

| Statistical analysis title | first Pulmonary Exacerbation Through Week 24 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Time to first pulmonary exacerbation through Week 24 was analyzed using Cox regression. The model included a covariate for treatment and adjustments for the age group and percent predicted forced expiratory volume in 1 second (FEV1) severity at baseline.

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0016 ^[7] |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 0.71 |

Notes:

[7] - Analyzed in sequence: test 1, primary ($\alpha=0.05$); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) ($\alpha=0.05$); test 3 using Hochberg's on time to pulmonary exacerbation (Wk 48) and weight (Wk 48).

| Statistical analysis title | first Pulmonary Exacerbation Through Week 48 |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Time to first pulmonary exacerbation through Week 48 was analyzed using Cox regression. The model included a covariate for treatment and adjustments for the age group and percent predicted forced expiratory volume in 1 second (FEV1) severity at baseline

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0012 ^[8] |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 0.73 |

Notes:

[8] - Analyzed in sequence: test 1, primary ($\alpha=0.05$); test 2, using Hochberg's step-up procedure on CFQ-R resp domain(Wk 24) and sweat chloride (Wk 24) ($\alpha=0.05$); test 3 using Hochberg's on time to pulmonary exacerbation (Wk 48) and weight (Wk 48).

Secondary: Absolute Change From Baseline in Weight at Week 24 and Week 48

| | |
|-----------------|--|
| End point title | Absolute Change From Baseline in Weight at Week 24 and Week 48 |
|-----------------|--|

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 population included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo) and had available assessments during the time frame.

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

End point timeframe:

Baseline to 24 weeks and 48 weeks

| End point values | Placebo | 150 mg Ivacaftor q12h | | |
|-------------------------------------|-----------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 83 | | |
| Units: kilograms | | | | |
| least squares mean (standard error) | | | | |
| At Week 24 | 0.2 (± 0.4) | 3 (± 0.4) | | |
| At Week 48 | 0.4 (± 0.5) | 3.1 (± 0.5) | | |

Statistical analyses

| | |
|----------------------------|-------------------|
| Statistical analysis title | Weight at Week 24 |
|----------------------------|-------------------|

Statistical analysis description:

At Week 24: Analysis for this variable was based on a linear mixed effects (LME) model with treatment as a fixed effect, and intercept, visit (days on study) and treatment by visit interaction as random effects, with adjustment for age group and baseline percent predicted forced expiratory volume in 1 second (FEV1) severity

| | |
|---|---------------------------------|
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.8 |
| upper limit | 3.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5 |

| | |
|--|---------------------------------|
| Statistical analysis title | Weight at Week 48 |
| Statistical analysis description: | |
| At Week 48: Analysis for this variable was based on a linear mixed effects (LME) model with treatment as a fixed effect and visit (days on study) and treatment by visit interaction as random effects, with adjustment for age group and baseline percent predicted forced expiratory volume in 1 second (FEV1) severity. | |
| Comparison groups | Placebo v 150 mg Ivacaftor q12h |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.3 |
| upper limit | 4.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For enrolled subjects, adverse events were collected through the Follow-up Visit (4 weeks [\pm 7 days] after the last dose of study drug).

Adverse event reporting additional description:

For subjects who were screened but were not subsequently enrolled in the study, non-serious adverse event (AEs) were not collected, but serious adverse events (SAEs) were reported. For subjects who completed 48 weeks of study drug treatment and enrolled in the open-label extension study, adverse events were only collected through the Week 48 Visit.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 12 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo-matched-to-ivacaftor tablet orally every 12 hours (q12h) up to 48 weeks.

| | |
|-----------------------|-----------------------|
| Reporting group title | 150 mg Ivacaftor q12h |
|-----------------------|-----------------------|

Reporting group description:

Ivacaftor 150 mg tablet orally every 12 hours (q12h) up to 48 weeks.

| Serious adverse events | Placebo | 150 mg Ivacaftor q12h | |
|---|------------------|-----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 33 / 78 (42.31%) | 20 / 83 (24.10%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cervix carcinoma | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Catheter Related Complication | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Testicular torsion | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 4 / 78 (5.13%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Cystic fibrosis lung | | | |
| subjects affected / exposed | 26 / 78 (33.33%) | 11 / 83 (13.25%) | |
| occurrences causally related to treatment / all | 4 / 37 | 3 / 22 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic pseudocyst | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting1 | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IgA nephropathy | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Pain in extremity subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Implant site infection subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection pseudomonal subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myringitis bullous subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | 150 mg Ivacaftor q12h | |
|---|-------------------|--------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 78 / 78 (100.00%) | 82 / 83 (98.80%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Peripheral Coldness | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Poor peripheral circulation | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 78 (11.54%) | 10 / 83 (12.05%) | |
| occurrences (all) | 11 | 13 | |

| | | |
|-------------------------------|----------------|----------------|
| Fatigue | | |
| subjects affected / exposed | 7 / 78 (8.97%) | 7 / 83 (8.43%) |
| occurrences (all) | 9 | 8 |
| Non-cardiac chest pain | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 2 / 83 (2.41%) |
| occurrences (all) | 4 | 3 |
| Chest discomfort | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Chills | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Malaise | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 2 | 0 |
| Pain | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Application site burn | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Application site dermatitis | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Application site scar | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Asthenia | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Axillary pain | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Catheter Related Complication | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|---|---------------------|---------------------|--|
| Catheter Thrombosis subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Chest pain subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Exercise tolerance decreased subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 1 / 83 (1.20%) 1 | |
| Food allergy subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 2 / 78 (2.56%) 2 | 0 / 83 (0.00%) 0 | |
| Balanitis subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Breast inflammation subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Breast Mass | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Gynaecomastia | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Nipple disorder | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Nipple pain | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Oligomenorrhoea | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 33 / 78 (42.31%) | 27 / 83 (32.53%) | |
| occurrences (all) | 59 | 38 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 15 / 78 (19.23%) | 17 / 83 (20.48%) | |
| occurrences (all) | 23 | 25 | |
| Nasal congestion | | | |
| subjects affected / exposed | 12 / 78 (15.38%) | 17 / 83 (20.48%) | |
| occurrences (all) | 17 | 22 | |
| Haemoptysis | | | |

| | | |
|--------------------------------|------------------|------------------|
| subjects affected / exposed | 15 / 78 (19.23%) | 9 / 83 (10.84%) |
| occurrences (all) | 21 | 17 |
| Productive cough | | |
| subjects affected / exposed | 11 / 78 (14.10%) | 12 / 83 (14.46%) |
| occurrences (all) | 19 | 15 |
| Rales | | |
| subjects affected / exposed | 8 / 78 (10.26%) | 9 / 83 (10.84%) |
| occurrences (all) | 14 | 17 |
| Respiratory tract congestion | | |
| subjects affected / exposed | 6 / 78 (7.69%) | 6 / 83 (7.23%) |
| occurrences (all) | 9 | 7 |
| Sinus congestion | | |
| subjects affected / exposed | 4 / 78 (5.13%) | 8 / 83 (9.64%) |
| occurrences (all) | 4 | 9 |
| Rhinorrhoea | | |
| subjects affected / exposed | 6 / 78 (7.69%) | 4 / 83 (4.82%) |
| occurrences (all) | 6 | 4 |
| Paranasal sinus hypersecretion | | |
| subjects affected / exposed | 6 / 78 (7.69%) | 3 / 83 (3.61%) |
| occurrences (all) | 7 | 3 |
| Wheezing | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 5 / 83 (6.02%) |
| occurrences (all) | 3 | 8 |
| Dyspnoea | | |
| subjects affected / exposed | 5 / 78 (6.41%) | 2 / 83 (2.41%) |
| occurrences (all) | 5 | 2 |
| Pleuritic pain | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 5 / 83 (6.02%) |
| occurrences (all) | 2 | 7 |
| Dysphonia | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 3 / 83 (3.61%) |
| occurrences (all) | 3 | 3 |
| Respiration abnormal | | |
| subjects affected / exposed | 4 / 78 (5.13%) | 2 / 83 (2.41%) |
| occurrences (all) | 5 | 2 |
| Epistaxis | | |

| | | |
|--|----------------|----------------|
| subjects affected / exposed | 1 / 78 (1.28%) | 3 / 83 (3.61%) |
| occurrences (all) | 1 | 4 |
| Lung hyperinflation | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 2 / 83 (2.41%) |
| occurrences (all) | 3 | 3 |
| Nasal mucosal disorder | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 2 |
| Increased viscosity of bronchial secretion | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Nasal inflammation | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 3 / 83 (3.61%) |
| occurrences (all) | 0 | 3 |
| Nasal turbinate abnormality | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 2 | 2 |
| Pharyngeal erythema | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 3 / 83 (3.61%) |
| occurrences (all) | 0 | 3 |
| Rhinitis allergic | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Rhonchi | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 4 |
| Asthma | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Postnasal Drip | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Pulmonary congestion | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |

| | | |
|------------------------------------|----------------|----------------|
| Sinus disorder | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Sputum discoloured | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 3 | 0 |
| Sputum retention | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Throat irritation | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Upper respiratory tract congestion | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Bronchial secretion retention | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Dyspnoea exertional | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypoventilation | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nasal oedema | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Nasal polyps | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Painful respiration | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Prolonged expiration | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |

| | | | |
|-----------------------------|----------------|----------------|--|
| Sneezing | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 3 / 83 (3.61%) | |
| occurrences (all) | 1 | 3 | |
| Abnormal dreams | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) | |
| occurrences (all) | 0 | 2 | |
| Libido decreased | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Affect lability | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Affective disorder | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Panic attack | | | |

| | | | |
|--------------------------------------|------------------|----------------|--|
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tobacco withdrawal symptoms | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 11 / 78 (14.10%) | 3 / 83 (3.61%) | |
| occurrences (all) | 14 | 3 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 5 / 78 (6.41%) | 5 / 83 (6.02%) | |
| occurrences (all) | 6 | 9 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 5 / 78 (6.41%) | 4 / 83 (4.82%) | |
| occurrences (all) | 6 | 4 | |
| Blood glucose increased | | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 5 / 83 (6.02%) | |
| occurrences (all) | 3 | 6 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 5 / 83 (6.02%) | |
| occurrences (all) | 2 | 7 | |
| Bacteria Sputum Identified | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 6 / 83 (7.23%) | |
| occurrences (all) | 1 | 7 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 4 / 83 (4.82%) | |
| occurrences (all) | 4 | 4 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 3 / 83 (3.61%) | |
| occurrences (all) | 4 | 6 | |
| Breath sounds abnormal | | | |
| subjects affected / exposed | 4 / 78 (5.13%) | 2 / 83 (2.41%) | |
| occurrences (all) | 5 | 2 | |
| Weight decreased | | | |

| | | |
|---|----------------|----------------|
| subjects affected / exposed | 4 / 78 (5.13%) | 2 / 83 (2.41%) |
| occurrences (all) | 4 | 2 |
| Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 2 / 83 (2.41%) |
| occurrences (all) | 4 | 5 |
| Sputum abnormal | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 3 / 83 (3.61%) |
| occurrences (all) | 2 | 3 |
| Urine leukocyte esterase positive | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 2 / 83 (2.41%) |
| occurrences (all) | 3 | 2 |
| Blood glucose decreased | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 1 / 83 (1.20%) |
| occurrences (all) | 4 | 1 |
| Blood urine present | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 2 / 83 (2.41%) |
| occurrences (all) | 3 | 2 |
| Prothrombin time prolonged | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 3 / 83 (3.61%) |
| occurrences (all) | 1 | 3 |
| Activated partial thromboplastin time prolonged | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 3 |
| Blood bilirubin increased | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 3 |
| Forced expiratory volume decreased | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 0 / 83 (0.00%) |
| occurrences (all) | 4 | 0 |
| International normalised ratio increased | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 1 |
| Vitamin D decreased | | |

| | | |
|---------------------------------------|----------------|----------------|
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| White blood cell count increased | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 0 / 83 (0.00%) |
| occurrences (all) | 4 | 0 |
| Blood glucose fluctuation | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Blood immunoglobulin E increased | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Glucose urine present | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Neutrophil count increased | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 6 | 0 |
| Bacterial Antibody Positive | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Blood immunoglobulin G increased | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Blood lactate dehydrogenase increased | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood urea increased | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Full blood count abnormal | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Fungus Sputum Test Positive | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |

| | | | |
|---------------------------------------|----------------|----------------|--|
| Gastrointestinal examination abnormal | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Liver palpable subcostal | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Monocyte count increased | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Protein urine present | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Specific gravity urine increased | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Spirometry abnormal | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight increased | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| ELECTROCARDIOGRAM ST-T CHANGE | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Joint Sprain | | | |
| subjects affected / exposed | 4 / 78 (5.13%) | 0 / 83 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 3 / 83 (3.61%) | |
| occurrences (all) | 0 | 3 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) | |
| occurrences (all) | 3 | 2 | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Burns second degree | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Concussion | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Medication error | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skeletal injury | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Stress fracture | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Sunburn | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Congenital, familial and genetic disorders | | | |
| Cystic fibrosis lung | | | |
| subjects affected / exposed | 39 / 78 (50.00%) | 29 / 83 (34.94%) | |
| occurrences (all) | 77 | 47 | |
| Cystic fibrosis related diabetes | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 3 / 83 (3.61%) | |
| occurrences (all) | 0 | 3 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 78 (16.67%) | 19 / 83 (22.89%) | |
| occurrences (all) | 31 | 39 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 10 / 83 (12.05%) | |
| occurrences (all) | 1 | 11 | |
| Sinus headache | | | |
| subjects affected / exposed | 4 / 78 (5.13%) | 6 / 83 (7.23%) | |
| occurrences (all) | 4 | 6 | |
| Migraine | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 3 / 83 (3.61%) | |
| occurrences (all) | 3 | 3 | |
| Lethargy | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Aphonia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cognitive disorder | | | |

| | | | |
|--------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dizziness postural | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Hemicephalalgia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyposmia | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 3 / 83 (3.61%) | |
| occurrences (all) | 2 | 3 | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Eosinophilia | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|---------------------|---------------------|--|
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Lymph node pain subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Lymphadenitis subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Ear discomfort subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 4 / 83 (4.82%) 4 | |
| Ear pain subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 3 / 83 (3.61%) 3 | |
| Deafness subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 1 / 83 (1.20%) 1 | |
| Tinnitus subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 2 / 83 (2.41%) 2 | |
| Ear congestion subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Ear pruritus subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Middle ear effusion subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Tympanic membrane hyperaemia subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Vestibular disorder | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Eye disorders | | | |
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 2 | 2 | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 78 (12.82%) | 13 / 83 (15.66%) | |
| occurrences (all) | 13 | 14 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 78 (11.54%) | 13 / 83 (15.66%) | |
| occurrences (all) | 12 | 22 | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 78 (12.82%) | 11 / 83 (13.25%) | |
| occurrences (all) | 12 | 12 | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 78 (12.82%) | 9 / 83 (10.84%) | |
| occurrences (all) | 10 | 13 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 78 (7.69%) | 4 / 83 (4.82%) | |
| occurrences (all) | 7 | 5 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 78 (6.41%) | 1 / 83 (1.20%) | |
| occurrences (all) | 5 | 1 | |
| Flatulence | | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 2 / 83 (2.41%) | |
| occurrences (all) | 5 | 2 | |
| Abdominal discomfort | | | |

| | | |
|--|----------------|----------------|
| subjects affected / exposed | 2 / 78 (2.56%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 1 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 1 |
| Toothache | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Abdominal distension | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 6 | 1 |
| Abdominal pain lower | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Faeces pale | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Gastritis | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Haemorrhoids | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 2 | 0 |
| Abdominal tenderness | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Distal intestinal obstruction syndrome | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| DRY MOUTH | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Dyspepsia | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |

| | | | |
|--|---------------------|------------------------|--|
| Frequent bowel movements subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Gastrointestinal motility disorder subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Inguinal hernia subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Pancreatitis subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Post-tussive vomiting subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Steatorrhoea subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Tooth impacted subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Hepatobiliary disorders Cytolytic Hepatitis subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 4 / 78 (5.13%) 4 | 12 / 83 (14.46%) 22 | |
| Acne subjects affected / exposed occurrences (all) | 3 / 78 (3.85%) 3 | 6 / 83 (7.23%) 6 | |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 78 (3.85%) 3 | 2 / 83 (2.41%) 2 | |
| Dry skin | | | |

| | | |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 3 / 78 (3.85%) | 1 / 83 (1.20%) |
| occurrences (all) | 3 | 1 |
| Erythema | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Night sweats | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Rash erythematous | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Rash macular | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 1 / 83 (1.20%) |
| occurrences (all) | 2 | 1 |
| Alopecia | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 1 |
| Eczema | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 4 | 0 |
| Rash maculo-papular | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 2 | 0 |
| Dermatitis | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Dermatitis acneiform | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Dermatitis contact | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Drug eruption | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Ecchymosis | | |

| | | | |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Hair texture abnormal | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Heat Rash | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoaesthesia Facial | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Photosensitivity Allergic Reaction | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Rosacea | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Skin irritation | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Chromaturia | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|----------------|----------------|--|
| Anuria | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Calculus ureteric | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Polyuria | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 78 (6.41%) | 7 / 83 (8.43%) | |
| occurrences (all) | 5 | 11 | |
| Back pain | | | |
| subjects affected / exposed | 5 / 78 (6.41%) | 5 / 83 (6.02%) | |
| occurrences (all) | 7 | 5 | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 4 / 83 (4.82%) | |
| occurrences (all) | 3 | 5 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 78 (3.85%) | 4 / 83 (4.82%) | |
| occurrences (all) | 5 | 4 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 4 / 83 (4.82%) | |
| occurrences (all) | 2 | 5 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) | |
| occurrences (all) | 1 | 2 | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Fibromyalgia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Flank pain | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) | |
| occurrences (all) | 1 | 1 | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epiphyseal disorder | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Finger deformity | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Jaw disorder | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Muscle atrophy | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle tightness | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Torticollis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |

| | | |
|---|------------------------|------------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 12 / 78 (15.38%) 16 | 19 / 83 (22.89%) 26 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 10 / 78 (12.82%) 14 | 10 / 83 (12.05%) 13 |
| Sinusitis subjects affected / exposed occurrences (all) | 7 / 78 (8.97%) 12 | 6 / 83 (7.23%) 8 |
| Rhinitis subjects affected / exposed occurrences (all) | 4 / 78 (5.13%) 4 | 6 / 83 (7.23%) 6 |
| Viral infection subjects affected / exposed occurrences (all) | 5 / 78 (6.41%) 5 | 2 / 83 (2.41%) 2 |
| Influenza subjects affected / exposed occurrences (all) | 3 / 78 (3.85%) 3 | 2 / 83 (2.41%) 2 |
| Pharyngitis subjects affected / exposed occurrences (all) | 3 / 78 (3.85%) 3 | 2 / 83 (2.41%) 2 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 4 / 83 (4.82%) 5 |
| Oral candidiasis subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 3 / 83 (3.61%) 4 |
| Ear infection subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 2 / 83 (2.41%) 2 |
| Pharyngitis streptococcal subjects affected / exposed occurrences (all) | 2 / 78 (2.56%) 2 | 1 / 83 (1.20%) 2 |
| Tooth infection subjects affected / exposed occurrences (all) | 3 / 78 (3.85%) 3 | 0 / 83 (0.00%) 0 |

| | | |
|---|----------------|----------------|
| Vulvovaginal mycotic infection | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 2 / 83 (2.41%) |
| occurrences (all) | 1 | 2 |
| Acute sinusitis | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Bacterial disease carrier | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Gastroenteritis | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 2 |
| Laryngitis | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 2 | 0 |
| Lung infection | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 2 / 83 (2.41%) |
| occurrences (all) | 0 | 6 |
| Respiratory tract infection viral | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 2 | 0 |
| Tooth abscess | | |
| subjects affected / exposed | 2 / 78 (2.56%) | 0 / 83 (0.00%) |
| occurrences (all) | 2 | 0 |
| Viral upper respiratory tract infection | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 1 / 83 (1.20%) |
| occurrences (all) | 1 | 2 |
| Abscess | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Bacterial infection | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Bronchiectasis | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|---|----------------|----------------|--|
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Bronchopulmonary aspergillosis allergic | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Conjunctivitis viral | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Dacryocystitis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Implant site infection | | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Labyrinthitis | | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) | |
| occurrences (all) | 0 | 1 | |
| Lice infestation | | | |

| | | |
|-----------------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Lower respiratory tract infection | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Onychomycosis | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Oral herpes | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Pancreas infection | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Paronychia | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Pneumonia bacterial | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Pulpitis dental | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Rhinovirus infection | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Skin infection | | |
| subjects affected / exposed | 1 / 78 (1.28%) | 0 / 83 (0.00%) |
| occurrences (all) | 1 | 0 |
| Sputum purulent | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Staphylococcal infection | | |
| subjects affected / exposed | 0 / 78 (0.00%) | 1 / 83 (1.20%) |
| occurrences (all) | 0 | 1 |
| Vaginal infection | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Viral pharyngitis subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 4 / 78 (5.13%) 4 | 3 / 83 (3.61%) 3 | |
| Decreased appetite subjects affected / exposed occurrences (all) | 2 / 78 (2.56%) 2 | 2 / 83 (2.41%) 2 | |
| Dehydration subjects affected / exposed occurrences (all) | 2 / 78 (2.56%) 2 | 1 / 83 (1.20%) 2 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 1 / 83 (1.20%) 1 | |
| Anorexia subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Gout subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Hypovitaminosis subjects affected / exposed occurrences (all) | 1 / 78 (1.28%) 1 | 0 / 83 (0.00%) 0 | |
| Polydipsia subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 78 (0.00%) 0 | 1 / 83 (1.20%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 17 April 2009 | Addition of a 24-week Extension Period for a total treatment duration of 48 weeks. Change to the secondary objective to evaluate the safety of VX-770 after both 24 weeks (original objective) and 48 weeks (newly added) of treatment. Addition of a secondary objective "To evaluate the efficacy of VX-770 after 48 weeks of treatment in subjects with CF who have the G551D-CFTR mutation on at least 1 allele". Addition of a secondary endpoint of "Absolute change from baseline in percent predicted FEV1 through Week 48". Addition of analysis of secondary and tertiary endpoints at Week 48. Addition of the option for subjects who complete 48 weeks of treatment to enroll in Study VX08-770-105. |
| 10 September 2009 | Addition of the tertiary endpoint of "Pulmonary exacerbations through Weeks 24 and 48". Changed few of the inclusion/exclusion criteria. Updated the version of the CTCAE used in the study for the grading of adverse events from Version 3.0 to Version 4.0. |
| 12 April 2010 | Changes in study procedures regarding liver function testing and considerations for study drug interruption and discontinuation to ensure the continued safety of subjects in this study. Updated the name of the safety department at Vertex from "Pharmacovigilance" to "Global Patient Safety" (throughout the protocol). Updated contact information. |
| 09 July 2010 | Based on feedback from the US Food and Drug Administration (FDA), an additional criterion for removal of subjects in the study was added to protocol: total bilirubin >2 ULN and/or clinical jaundice, in association with elevation of ALT or AST >3 ULN. Additional clarification of the intended analysis were provided. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22047557>