# Clinical trial results:
# A Phase 3, Two-Arm, Rollover Study to Evaluate the Safety of Long-Term Ivacaftor Treatment in Subjects 6 Years of Age and Older with Cystic
# Fibrosis and a Non-G551D CFTR Mutation

## Summary

| | |
|---|---|
| EudraCT number | 2012-000389-39 |
| Trial protocol | GB BE |
| Global end of trial date | 18 April 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 02 November 2016 |
| First version publication date | 02 November 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | VX12-770-112 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01707290 |
| 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, +1 617-341-677, medicalinfo@vrtx.com |
| Scientific contact | Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617-341-6777, medicalinfo@vrtx.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-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 | 30 August 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 18 April 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety of long-term ivacaftor treatment in subjects with cystic fibrosis (CF).

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 | 13 February 2013 |
| 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? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 93 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | United Kingdom: 15 |
| Worldwide total number of subjects | 125 |
| EEA total number of subjects | 32 |

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) | 22 |
| Adolescents (12-17 years) | 12 |
| Adults (18-64 years) | 89 |

| | |
|---|---|
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study consisted of 2 arms: Ivacaftor arm and Observational arm. The Ivacaftor arm enrolled subjects from Study VX11-770-110 (2012-000387-19), Study VX12-770-111 (2012-000388-26) and Study VX12-770-113. The Observational arm enrolled subjects from Study VX11-770-110 (2012-000387-19) and Study VX12-770-111 (2012-000388-26).

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ivacaftor arm |

Arm description:

Subjects who received Ivacaftor 150 milligram (mg) tablet and/or Placebo matched to ivacaftor tablet every 12 hours (q12h) in the previous study VX11-770-110 (Study 110; 2012-000387-19), VX12-770-111 (Study 111; 2012-000388-26) or VX12-770-113 (Study 113); received Ivacaftor 150 mg tablet q12h in this VX12-770-112 (Study 112; 2012-000389-39) up to 104 weeks.

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

Dosage and administration details:

Ivacaftor 150 mg tablet q12h for 104 weeks.

| | |
|---|---|
| **Arm title** | Observational arm |

Arm description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110 or Study 111, were observed (did not receive study drug) in this Study 112 for up to 2 years.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | Ivacaftor arm | Observational arm |
|---|---|---|
| Started | 121 | 4 |
| Completed | 35 | 3 |
| Not completed | 86 | 1 |
| Commercial drug available | 60 | 1 |
| Physician decision | 1 | - |
| Adverse Event (AE) | 1 | - |

| | | |
|---|---|---|
| Other unspecified | 17 | - |
| Withdrawal of Consent (Not Due to AE) | 4 | - |
| Lost to follow-up | 3 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ivacaftor arm |
| Reporting group description: | |
| Subjects who received Ivacaftor 150 milligram (mg) tablet and/or Placebo matched to ivacaftor tablet every 12 hours (q12h) in the previous study VX11-770-110 (Study 110; 2012-000387-19), VX12-770-111 (Study 111; 2012-000388-26) or VX12-770-113 (Study 113); received Ivacaftor 150 mg tablet q12h in this VX12-770-112 (Study 112; 2012-000389-39) up to 104 weeks. | |
| Reporting group title | Observational arm |
| Reporting group description: | |
| Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110 or Study 111, were observed (did not receive study drug) in this Study 112 for up to 2 years. | |

| Reporting group values | Ivacaftor arm | Observational arm | Total |
|---|---|---|---|
| Number of subjects | 121 | 4 | 125 |
| Age categorical<br>Units: Subjects | | | |
| 6 to 11 years | 21 | 1 | 22 |
| 12 to 17 years | 11 | 1 | 12 |
| 18 years and over | 89 | 2 | 91 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 61 | 3 | 64 |
| Male | 60 | 1 | 61 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Ivacaftor arm |

Reporting group description:

Subjects who received Ivacaftor 150 milligram (mg) tablet and/or Placebo matched to ivacaftor tablet every 12 hours (q12h) in the previous study VX11-770-110 (Study 110; 2012-000387-19), VX12-770-111 (Study 111; 2012-000388-26) or VX12-770-113 (Study 113); received Ivacaftor 150 mg tablet q12h in this VX12-770-112 (Study 112; 2012-000389-39) up to 104 weeks.

| | |
|---|---|
| Reporting group title | Observational arm |

Reporting group description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110 or Study 111, were observed (did not receive study drug) in this Study 112 for up to 2 years.

| | |
|---|---|
| Subject analysis set title | Ivacaftor arm: Study 110 |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study 110; received Ivacaftor 150 mg tablet q12h in this Study 112 up to 104 weeks.

| | |
|---|---|
| Subject analysis set title | Ivacaftor arm: Study 111 |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study  111; received Ivacaftor 150 mg tablet q12h in this Study 112 up to 104 weeks.

| | |
|---|---|
| Subject analysis set title | Ivacaftor arm: Study 113 |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous Study  113; received Ivacaftor 150 mg tablet q12h in this Study 112 up to 104 weeks.

### Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs) in Ivacaftor arm

| | |
|---|---|
| End point title | Number of Subjects With Treatment Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs) in Ivacaftor arm[1][2] |

End point description:

AE: any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after informed consent form is signed. AE includes serious as well as non-serious AEs. SAE (subset of AE): medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, In-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. TEAEs were defined as adverse events with start date or increased severity on and after the first dose of study drug through Week 108. Safety Set included all subjects who received at least 1 dose of study drug (ivacaftor).

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Day 1 up to Week 108

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were reported, inferential statistics were not planned for primary endpoint.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

| End point values | Ivacaftor arm | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 121 | | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| Subjects with AEs | 117 | | | |
| Subjects with SAEs | 27 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96, and 104

| End point title | Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96, and 104 |
|---|---|

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Hankinson and Wang standards were used to calculate percent predicted FEV1 (for age, gender, and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 6 to 17 years and for female subjects aged 6 to 15 years. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). Full Analysis Set (FAS) included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm, respectively.

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

End point timeframe:

Baseline, Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 (Study 112)

| End point values | Ivacaftor arm: Study 110 | Ivacaftor arm: Study 111 | Ivacaftor arm: Study 113 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 65 | 35 | 21 | |
| Units: Percent predicted of FEV1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 65, 35, 21) | 71.8 (± 20.4) | 78.3 (± 21.1) | 62.8 (± 22.2) | |
| Change at Week 2 (n= 65, 35, 21) | 3.8 (± 8) | 4.4 (± 7.7) | 4 (± 7.2) | |
| Change at Week 12 (n=63, 33, 21) | 5.4 (± 8.9) | 5.5 (± 8.3) | 4.9 (± 6.7) | |
| Change at Week 24 (n= 62, 34, 21) | 4.5 (± 8.4) | 7.1 (± 8.3) | 4.6 (± 8.5) | |
| Change at Week 36 (n= 60, 29, 20) | 4.4 (± 7.1) | 7.5 (± 8.2) | 4.9 (± 8.2) | |
| Change at Week 48 (n= 58, 19, 20) | 4.4 (± 7.5) | 6.4 (± 10.7) | 4.9 (± 9) | |
| Change at Week 60 (n= 58, 16, 20) | 4.5 (± 8.4) | 8.2 (± 8.3) | 4.5 (± 8.8) | |
| Change at Week 72 (n= 50, 13, 18) | 3.6 (± 8.9) | 7.8 (± 9.2) | 5.9 (± 9.2) | |
| Change at Week 84 (n= 40, 11, 16) | 5.4 (± 13.5) | 7.7 (± 7.6) | 4.8 (± 7.2) | |
| Change at Week 96 (n= 28, 9, 15) | 4.1 (± 14.6) | 9.9 (± 6.4) | 5.9 (± 8.1) | |
| Change at Week 104 (n= 20, 9, 12) | 4.6 (± 13.2) | 4.9 (± 5.8) | 6.3 (± 10) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change From Baseline in Body Mass Index (BMI) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104

| End point title | Absolute Change From Baseline in Body Mass Index (BMI) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 |
|---|---|

End point description:

BMI was defined as weight in kg divided by height in m^2. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). FAS included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm, respectively.

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

End point timeframe:

Baseline, Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 (Study 112)

| End point values | Ivacaftor arm: Study 110 | Ivacaftor arm: Study 111 | Ivacaftor arm: Study 113 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 65 | 35 | 21 | |
| Units: kilogram per square meter (kg/m^2) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 65, 35, 21) | 23.75 (± 5.63) | 23.15 (± 5.28) | 24.81 (± 5.76) | |
| Change at Week 2 (n= 65, 35, 21) | 0.06 (± 0.43) | 0.16 (± 0.47) | 0.07 (± 0.43) | |
| Change at Week 12 (n= 64, 35, 21) | 0.32 (± 0.59) | 0.39 (± 0.62) | 0.22 (± 0.6) | |
| Change at Week 24 (n= 62, 35, 21) | 0.43 (± 0.92) | 0.65 (± 0.96) | 0.17 (± 0.91) | |
| Change at Week 36 (n= 60, 29, 20) | 0.62 (± 1.04) | 0.64 (± 1.07) | 0.02 (± 1.27) | |
| Change at Week 48 (n=59, 19, 20) | 0.54 (± 1.39) | 0.58 (± 1.22) | 0.28 (± 1.26) | |
| Change at Week 60 (n= 58, 16, 20) | 0.72 (± 1.32) | 0.25 (± 1.09) | 0.38 (± 1.22) | |
| Change at Week 72 (n= 51, 13, 17) | 1.05 (± 1.73) | 0.45 (± 1.34) | 0.22 (± 1.22) | |
| Change at Week 84 (n= 40, 11, 16) | 0.72 (± 1.51) | 0.33 (± 1.42) | 0.23 (± 0.92) | |
| Change at Week 96 (n= 28, 9, 16) | 0.49 (± 1.44) | 0.1 (± 1.49) | 0.52 (± 1.28) | |
| Change at Week 104 (n= 20, 9, 12) | 0.42 (± 1.49) | 0.16 (± 1.37) | 0.88 (± 1.39) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change From Baseline in Sweat Chloride at Week 2, 24, 48 and 104

| End point title | Absolute Change From Baseline in Sweat Chloride at Week 2, 24, 48 and 104 |
|---|---|

End point description:

Sweat samples were collected using an approved collection device. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). FAS included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "Number of subjects analysed" signifies those subjects who were evaluable for this outcome and "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm respectively.

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

End point timeframe:

Baseline, Week 2, 24, 48 and 104 (Study 112)

| **End point values** | Ivacaftor arm: Study 110 | Ivacaftor arm: Study 111 | Ivacaftor arm: Study 113 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 59 | 33 | 21 | |
| Units: millimole per liter (mmol/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=59, 33, 21) | 60.9 (± 19.4) | 80.2 (± 22.8) | 55.7 (± 22.2) | |
| Change at Week 2 (n=59, 31, 21) | -19.3 (± 10.7) | -38.4 (± 27.5) | -4.5 (± 10.9) | |
| Change at Week 24 (n=56, 33, 20) | -13 (± 18.4) | -39.2 (± 27) | 1.1 (± 15.8) | |
| Change at Week 48 (n=50, 19, 19) | -13.5 (± 16.2) | -40.6 (± 26.1) | -1.9 (± 17.8) | |
| Change at Week 104 (n=15, 9, 11) | -13.7 (± 22.9) | -32.9 (± 26.8) | 5.4 (± 18.1) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change From Baseline in Respiratory Domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104

| End point title | Absolute Change From Baseline in Respiratory Domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R) at Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 |
|---|---|

End point description:

The CFQ-R is a validated subject reported outcome measuring health related quality of life for subjects with CF. 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. Baseline was defined as the most recent measurement before intake of the first dose of study drug (ivacaftor) in Study 112 (2012-000389-39). FAS included all subjects who received at least 1 dose of study drug (ivacaftor). Here, "n" signifies those subjects who were evaluable for this measure at the specified time point for each arm respectively.

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

End point timeframe:

Baseline, Week 2, 12, 24, 36, 48, 60, 72, 84, 96 and 104 (Study 112)

| End point values | Ivacaftor arm: Study 110 | Ivacaftor arm: Study 111 | Ivacaftor arm: Study 113 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 65 | 35 | 21 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n= 65, 35, 21) | 68.6 (± 21.6) | 72.4 (± 20.3) | 65.9 (± 18.8) | |
| Change at Week 2 (n= 65, 35, 21) | 5.5 (± 17.9) | 4.5 (± 17.5) | 13.2 (± 16.2) | |
| Change at Week 12 (n= 64, 35, 21) | 11.6 (± 18) | 5.7 (± 18.5) | 13.5 (± 20) | |
| Change at Week 24 (n= 62, 35, 21) | 6.7 (± 19) | 3.4 (± 18.7) | 8.5 (± 14.9) | |
| Change at Week 36 (n=60, 29, 20) | 12.1 (± 19.3) | 5.7 (± 13.8) | 7.9 (± 20.5) | |
| Change at Week 48 (n= 59, 19, 20) | 9.5 (± 17.6) | 4.4 (± 13.2) | 11.4 (± 15.7) | |
| Change at Week 60 (n= 57, 15, 20) | 7.1 (± 18.6) | 4.4 (± 10.9) | 8.6 (± 19.3) | |
| Change at Week 72 (n= 51, 13, 18) | 10.4 (± 22.2) | 5.6 (± 11.8) | 8.6 (± 19) | |
| Change at Week 84 (n= 40, 11, 16) | 10.5 (± 19.5) | 8.8 (± 14.1) | 4.9 (± 14.6) | |
| Change at Week 96 (n= 28, 9, 16) | 8.8 (± 21.1) | 0 (± 9.5) | 9.4 (± 14.7) | |
| Change at Week 104 (n= 20, 9, 12) | 9.2 (± 14) | 1.9 (± 8.8) | 19.9 (± 16) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Pulmonary Exacerbations Events

| End point title | Number of Pulmonary Exacerbations Events |
|---|---|

End point description:

Pulmonary exacerbation events include those events which require treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. The number of events were reported. FAS included all subjects who received at least 1 dose of study drug (ivacaftor).

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

End point timeframe:

Through Week 104

| End point values | Ivacaftor arm: Study 110 | Ivacaftor arm: Study 111 | Ivacaftor arm: Study 113 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 65 | 35 | 21 | |
| Units: pulmonary exacerbation events | | | | |
| number (not applicable) | 47 | 30 | 6 | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With SAEs in Observational arm

| End point title | Number of Subjects With SAEs in Observational arm[3] |
|---|---|

End point description:

SAE was defined as a medical event or condition, which falls into any of the following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, In-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. Analysis population included all subjects who were included in the observational arm.

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

End point timeframe:

up to 2 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms which are applicable to the endpoint are reported.

| **End point values** | Observational arm | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 | | | |
| Units: subjects | | | | |
| number (not applicable) | 1 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 108 for Ivacaftor arm; up to 2 years for Observational arm

Adverse event reporting additional description:

Non-SAEs were not collected for Observational arm. Only SAEs were planned to be collected for the Observational arm.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ivacaftor arm |

Reporting group description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous study 110 (2012-000387-19) or study 111 (2012-000388-26) or study 113, received Ivacaftor 150 mg tablet q12h in this study 112 (2012-000389-39) up to 104 weeks.

| | |
|---|---|
| Reporting group title | Observational arm |

Reporting group description:

Subjects who received Ivacaftor 150 mg tablet and/or Placebo matched to ivacaftor tablet q12h in the previous study 110 (2012-000387-19) or study 111 (2012-000388-26), were observed (did not receive study drug) in this study 112 (2012-000389-39) for up to 2 years.

| Serious adverse events | Ivacaftor arm | Observational arm | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 121 (22.31%) | 1 / 4 (25.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Influenza A virus test positive | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiomyopathy acute | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (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 | 1 / 121 (0.83%) | 0 / 4 (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 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (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 | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (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 | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 21 / 121 (17.36%) | 1 / 4 (25.00%) | |
| occurrences causally related to treatment / all | 1 / 34 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Ivacaftor arm | Observational arm | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 117 / 121 (96.69%) | 0 / 4 (0.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Seborrhoeic keratosis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin papilloma | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thyroid neoplasm | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pallor | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 121 (14.05%) | 0 / 4 (0.00%) | |
| occurrences (all) | 25 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 121 (9.92%) | 0 / 4 (0.00%) | |
| occurrences (all) | 15 | 0 | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |

| | | | |
|---|---|---|---|
| Influenza like illness | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Chills | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Feeling of body temperature change | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pain | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Device leakage | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Implant site rash | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Local swelling | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vaccination site pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune system disorders | | | |
| Seasonal allergy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Amenorrhoea | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Breast pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Testicular torsion | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal discomfort | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 41 / 121 (33.88%) | 0 / 4 (0.00%) | |
| occurrences (all) | 81 | 0 | |
| Sputum increased | | | |
| subjects affected / exposed | 22 / 121 (18.18%) | 0 / 4 (0.00%) | |
| occurrences (all) | 27 | 0 | |
| Sinus congestion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 22 / 121 (18.18%) | 0 / 4 (0.00%) | |
| occurrences (all) | 34 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 18 / 121 (14.88%) | 0 / 4 (0.00%) | |
| occurrences (all) | 24 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 17 / 121 (14.05%) | 0 / 4 (0.00%) | |
| occurrences (all) | 20 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 12 / 121 (9.92%) | 0 / 4 (0.00%) | |
| occurrences (all) | 14 | 0 | |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 9 / 121 (7.44%) | 0 / 4 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 12 / 121 (9.92%) | 0 / 4 (0.00%) | |
| occurrences (all) | 25 | 0 | |
| Wheezing | | | |
| subjects affected / exposed | 9 / 121 (7.44%) | 0 / 4 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Rales | | | |
| subjects affected / exposed | 7 / 121 (5.79%) | 0 / 4 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 0 / 4 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Paranasal sinus hypersecretion | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 0 / 4 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 0 / 4 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Respiration abnormal | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Nasal polyps | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Throat irritation | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nasal mucosal disorder | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Productive cough | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Increased viscosity of bronchial secretion | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung hyperinflation | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal inflammation | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Nasal oedema | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Painful respiration | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Prolonged expiration | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory tract irritation | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus polyp | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sneezing | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sputum discoloured | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Throat tightness | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 0 / 4 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Insomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Depression | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tobacco abuse | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Drug dependence | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Bacterial test positive | | | |
| subjects affected / exposed | 7 / 121 (5.79%) | 0 / 4 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 0 / 4 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 0 / 4 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Haemophilus test positive | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Atypical mycobacterium test positive | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Body temperature increased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pseudomonas test positive | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Vitamin D decreased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood calcium decreased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Crystal urine present | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza A virus test positive | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flavobacterium test positive | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Klebsiella test positive | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Streptococcus test positive | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ultrasound biliary tract abnormal | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary sediment present | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urine analysis abnormal | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitamin A decreased | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| White blood cells urine positive | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Laceration | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Muscle strain | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Arthropod sting | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epicondylitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fall | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ligament rupture | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Snake bite | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skeletal injury | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 23 / 121 (19.01%) | 0 / 4 (0.00%) | |
| occurrences (all) | 38 | 0 | |
| Sinus headache | | | |
| subjects affected / exposed | 9 / 121 (7.44%) | 0 / 4 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 121 (5.79%) | 0 / 4 (0.00%) | |
| occurrences (all) | 8 | 0 | |

| | | | |
|---|---|---|---|
| Migraine | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Burning sensation | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperaesthesia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypersomnia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Tinnitus | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Middle ear effusion | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Otorrhoea | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vertigo | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blepharospasm | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Conjunctivitis allergic | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye swelling | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Photophobia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 17 / 121 (14.05%) | 0 / 4 (0.00%) | |
| occurrences (all) | 24 | 0 | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 121 (14.05%) | 0 / 4 (0.00%) | |
| occurrences (all) | 25 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 12 / 121 (9.92%) | 0 / 4 (0.00%) | |
| occurrences (all) | 18 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 12 / 121 (9.92%) | 0 / 4 (0.00%) | |
| occurrences (all) | 13 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 121 (7.44%) | 0 / 4 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 7 / 121 (5.79%) | 0 / 4 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 0 / 4 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Tooth impacted | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dental caries | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Flatulence | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Steatorrhoea | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Toothache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Barrett's oesophagus | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Defaecation urgency | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dental discomfort | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Frequent bowel movements | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Palatal disorder | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Proctitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rectal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rectal polyp | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth loss | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 0 / 4 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Eczema | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Rash erythematous | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dermatitis contact | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyperhidrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Eczema nummular | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rosacea | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Subcutaneous nodule | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Acne | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 9 / 121 (7.44%) | 0 / 4 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 6 / 121 (4.96%) | 0 / 4 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 0 / 4 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Osteopenia | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Arthritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Clubbing | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metatarsalgia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Monarthritis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |

| | | | | |
|---|---|---|---|---|
| Infective pulmonary exacerbation of cystic fibrosis | | | | |
| subjects affected / exposed | 49 / 121 (40.50%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 85 | 0 | | |
| Nasopharyngitis | | | | |
| subjects affected / exposed | 21 / 121 (17.36%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 32 | 0 | | |
| Sinusitis | | | | |
| subjects affected / exposed | 18 / 121 (14.88%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 35 | 0 | | |
| Viral upper respiratory tract infection | | | | |
| subjects affected / exposed | 17 / 121 (14.05%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 23 | 0 | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 15 / 121 (12.40%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 19 | 0 | | |
| Gastroenteritis viral | | | | |
| subjects affected / exposed | 9 / 121 (7.44%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 9 | 0 | | |
| Oral candidiasis | | | | |
| subjects affected / exposed | 8 / 121 (6.61%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 13 | 0 | | |
| Influenza | | | | |
| subjects affected / exposed | 7 / 121 (5.79%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 9 | 0 | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 6 | 0 | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 5 / 121 (4.13%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 6 | 0 | | |
| Acute sinusitis | | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | | |
| occurrences (all) | 6 | 0 | | |
| Vulvovaginal mycotic infection | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 121 (2.48%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Bronchopulmonary aspergillosis allergic | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Otitis externa | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pharyngitis bacterial | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear lobe infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Folliculitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Furuncle | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemophilus infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infected dermal cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laryngitis viral | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myringitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal abscess | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oesophagitis bacterial | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Staphylococcal skin infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vaginitis bacterial | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral pharyngitis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 121 (1.65%) | 0 / 4 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 4 / 121 (3.31%) | 0 / 4 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Fluid retention | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Impaired fasting glucose | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Increased appetite | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitamin A deficiency | | | |
| subjects affected / exposed | 1 / 121 (0.83%) | 0 / 4 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 March 2012 | Clarified sample collection, statistical analysis plan and Early Termination visit details; updated follow-up timeframe; corrected pharmacogenomic analysis text. |
| 05 December 2012 | Extended study duration to 2 years; secondary objective was changed to evaluate the post-treatment safety of ivacaftor in subjects enrolled in the observational arm; pharmacokinetic (PK) blood sample collection was added to the ivacaftor arm; ophthalmologic examination was added to the safety endpoints and additional ophthalmologic examinations were added; contraceptive requirements were clarified; included a planned interim analysis for safety and efficacy data after all subjects completed Week 24 Visit. |
| 01 April 2013 | Subjects from Study 113 were offered enrollment in the ivacaftor arm of Study 112; clarified timing of Day 1 Visit in Study 112 with respect to Study 113; clarified that PK blood samples would not be collected from Study 113 subjects. |
| 29 July 2013 | Clarified that subjects from Study 113 must have completed the Study 113 Follow-up Visit and met responder criteria for eligibility to enroll in the Study 112 ivacaftor arm. |
| 13 February 2014 | Pregnancy language was revised; changed protocol to allow subjects to discontinue the study when Kalydeco was commercially-available and reimbursed for that indication in the subject's country; added optional exploratory hypertonic saline substudy; changed the timing of the planned interim analysis. |
| 29 July 2014 | Added an optional exploratory substudy for subjects with the G970R-CFTR Mutation. |
| 08 December 2014 | Made ophthalmologic examination assessments applicable to all subjects. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported