



## Clinical trial results:

### A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis who Have the R117H-CFTR Mutation

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2012-000387-19  |
| Trial protocol           | GB              |
| Global end of trial date | 25 October 2013 |

#### 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 | VX11-770-110 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01614457 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | 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                       | 19 November 2013 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 25 October 2013  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of ivacaftor in subjects (6 years of age and older) with cystic fibrosis (CF) with R117H-CF transmembrane conductance regulator (CFTR) mutation.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy:

Subjects remained on their stable CF medication regimens from 4 weeks before Day 1 through the Follow up Visit.

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 03 July 2012 |
| 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: 15 |
| Country: Number of subjects enrolled | United States: 54  |
| Worldwide total number of subjects   | 69                 |
| EEA total number of subjects         | 15                 |

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)                     | 17 |
| Adolescents (12-17 years)                 | 2  |
| Adults (18-64 years)                      | 48 |

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

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 27 sites in the United States and the European Union.

### Pre-assignment

Screening details:

A total of 70 subjects were randomized, of which 1 subject discontinued the study prior to study drug administration. A total of 69 subjects started treatment.

### 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       |
| <b>Arm title</b>             | Ivacaftor |

Arm description:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.

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

Dosage and administration details:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.

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

Dosage and administration details:

Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.

| <b>Number of subjects in period 1</b> | Ivacaftor | Placebo |
|---------------------------------------|-----------|---------|
| Started                               | 34        | 35      |
| Completed                             | 32        | 35      |
| Not completed                         | 2         | 0       |
| 'Non-Compliance '                     | 1         | -       |
| 'Pregnancy (Self or Partner) '        | 1         | -       |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks.

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

Reporting group description:

Placebo matched to ivacaftor tablet orally twice daily for 24 weeks.

| Reporting group values                                                  | Ivacaftor       | Placebo         | Total |
|-------------------------------------------------------------------------|-----------------|-----------------|-------|
| Number of subjects                                                      | 34              | 35              | 69    |
| Age categorical<br>Units: Subjects                                      |                 |                 |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 29.2<br>± 16.57 | 32.7<br>± 17.43 | -     |
| Gender categorical<br>Units: Subjects                                   |                 |                 |       |
| Female                                                                  | 19              | 20              | 39    |
| Male                                                                    | 15              | 15              | 30    |

## End points

### End points reporting groups

|                                                                                                      |           |
|------------------------------------------------------------------------------------------------------|-----------|
| Reporting group title                                                                                | Ivacaftor |
| Reporting group description:<br>Ivacaftor 150 milligram (mg) tablet orally twice daily for 24 weeks. |           |
| Reporting group title                                                                                | Placebo   |
| Reporting group description:<br>Placebo matched to ivacaftor tablet orally twice daily for 24 weeks. |           |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24 |
| End point description:<br>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.<br><br>The analysis was performed on Full Analysis Set (FAS) which included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). |                                                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Primary                                                                                                        |
| End point timeframe:<br>Baseline, Week 24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                |

| End point values                    | Ivacaftor              | Placebo                |  |  |
|-------------------------------------|------------------------|------------------------|--|--|
| Subject group type                  | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed         | 34                     | 35                     |  |  |
| Units: Percent predicted of FEV1    |                        |                        |  |  |
| least squares mean (standard error) | 2.5724 ( $\pm$ 1.1532) | 0.4611 ( $\pm$ 1.1313) |  |  |

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                   |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                        | Ivacaftor vs Placebo |
| Statistical analysis description:<br>Analysis was based on mixed effects model for repeated measures (MMRM) with dependent variable absolute change from baseline, with treatment group, visit and treatment by visit interaction as fixed effects, subject as random effect, and with adjustment for the continuous baseline value of age and percent predicted FEV1, using compound symmetry covariance matrix. |                      |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                 | Ivacaftor v Placebo  |

|                                         |                                   |
|-----------------------------------------|-----------------------------------|
| Number of subjects included in analysis | 69                                |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.1979                          |
| Method                                  | Mixed Model Repeated Measures     |
| Parameter estimate                      | Least square (LS) Mean Difference |
| Point estimate                          | 2.1114                            |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -1.1305                           |
| upper limit                             | 5.3532                            |

## Secondary: Change From Baseline in Body Mass Index (BMI) at Week 24

|                                                                                                         |                                                          |
|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| End point title                                                                                         | Change From Baseline in Body Mass Index (BMI) at Week 24 |
| End point description:                                                                                  |                                                          |
| BMI was defined as weight in kilogram (kg) divided by height in square meter (m <sup>2</sup> ).         |                                                          |
| FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). |                                                          |
| End point type                                                                                          | Secondary                                                |
| End point timeframe:                                                                                    |                                                          |
| Baseline, Week 24                                                                                       |                                                          |

| End point values                    | Ivacaftor        | Placebo           |  |  |
|-------------------------------------|------------------|-------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed         | 34               | 35                |  |  |
| Units: kg/m <sup>2</sup>            |                  |                   |  |  |
| least squares mean (standard error) | 0.491 (± 0.6653) | 0.2284 (± 0.6504) |  |  |

## Statistical analyses

|                                                                                                                                                                                                                                                                               |                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                    | Ivacaftor vs Placebo   |
| Statistical analysis description:                                                                                                                                                                                                                                             |                        |
| Analysis was based on linear mixed model with dependent variable BMI and treatment as a fixed effect, adjustment for baseline percent predicted FEV1, age and visit by treatment interaction was included as covariates and intercept, visit were included as random effects. |                        |
| Comparison groups                                                                                                                                                                                                                                                             | Ivacaftor v Placebo    |
| Number of subjects included in analysis                                                                                                                                                                                                                                       | 69                     |
| Analysis specification                                                                                                                                                                                                                                                        | Pre-specified          |
| Analysis type                                                                                                                                                                                                                                                                 | superiority            |
| P-value                                                                                                                                                                                                                                                                       | = 0.778 <sup>[1]</sup> |
| Method                                                                                                                                                                                                                                                                        | Linear Mixed Model     |
| Parameter estimate                                                                                                                                                                                                                                                            | LS Mean difference     |
| Point estimate                                                                                                                                                                                                                                                                | 0.2626                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1.5698 |
| upper limit         | 2.095   |

Notes:

[1] - p-value for the treatment effect is from the slope of BMI versus time.

## Secondary: Change From Baseline in Sweat Chloride Through Week 24

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Change From Baseline in Sweat Chloride Through Week 24 |
|-----------------|--------------------------------------------------------|

End point description:

Sweat samples were collected using an approved Macroduct (Wescor, Logan, Utah) collection device. A volume of greater than or equal to ( $\geq$ ) 15 microliter was required for determination of sweat chloride.

FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). Here, "Number of subjects analyzed" signifies those subjects who were evaluable for this measure.

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

End point timeframe:

Baseline, Week 24

| End point values                    | Ivacaftor                | Placebo                 |  |  |
|-------------------------------------|--------------------------|-------------------------|--|--|
| Subject group type                  | Reporting group          | Reporting group         |  |  |
| Number of subjects analysed         | 32                       | 35                      |  |  |
| Units: millimole per liter (mmol/L  |                          |                         |  |  |
| least squares mean (standard error) | -26.2771 ( $\pm$ 1.4584) | -2.3078 ( $\pm$ 1.3716) |  |  |

## Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Ivacaftor vs Placebo |
|----------------------------|----------------------|

Statistical analysis description:

Analysis was based on MMRM with dependent variable absolute change from baseline, with treatment group, visit and treatment by visit interaction as fixed effects, subject as random effect, and with adjustment for the continuous baseline value of age and percent predicted FEV1, and sweat chloride, using a compound symmetry covariance matrix.

|                                         |                               |
|-----------------------------------------|-------------------------------|
| Comparison groups                       | Ivacaftor v Placebo           |
| Number of subjects included in analysis | 67                            |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | < 0.0001                      |
| Method                                  | Mixed Model Repeated Measures |
| Parameter estimate                      | LS Mean difference            |
| Point estimate                          | -23.9693                      |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -28.0094                      |
| upper limit                             | -19.9293                      |

## Secondary: Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 24

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

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms (for example, coughing, congestion, wheezing), score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life.

FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo). Here, "Number of participants analyzed" signifies those subjects who were evaluable for this measure.

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

End point timeframe:

Baseline, Week 24

| End point values                    | Ivacaftor              | Placebo                 |  |  |
|-------------------------------------|------------------------|-------------------------|--|--|
| Subject group type                  | Reporting group        | Reporting group         |  |  |
| Number of subjects analysed         | 33                     | 34                      |  |  |
| Units: units on a scale             |                        |                         |  |  |
| least squares mean (standard error) | 7.5585 ( $\pm$ 2.2073) | -0.8289 ( $\pm$ 2.1569) |  |  |

## Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Ivacaftor vs Placebo |
|----------------------------|----------------------|

Statistical analysis description:

Analysis was based on MMRM with dependent variable absolute change from baseline, with treatment group, visit and treatment by visit interaction as fixed effects, subject as random effect, and with adjustment for the continuous baseline value of age and percent predicted FEV1, and CFQ-R respiratory domain score, using compound symmetry covariance matrix.

|                                         |                               |
|-----------------------------------------|-------------------------------|
| Comparison groups                       | Ivacaftor v Placebo           |
| Number of subjects included in analysis | 67                            |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.0091                      |
| Method                                  | Mixed Model Repeated Measures |
| Parameter estimate                      | LS Mean difference            |
| Point estimate                          | 8.3874                        |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 2.1658                        |
| upper limit                             | 14.609                        |

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**Secondary: Time to First Pulmonary Exacerbation**

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|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Time to First Pulmonary Exacerbation |
|-----------------|--------------------------------------|

End point description:

Number of events (pulmonary exacerbation) during the pre-specified time intervals were reported. A subject without an exacerbation before withdrawal from the study was considered censored at the time of withdrawal, and a subject without an exacerbation who completes the study period was considered censored at the end of the analysis period.

FAS included all randomized subjects who received at least 1 dose of study drug (ivacaftor or placebo).

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

End point timeframe:

Day 0 to 15, Day 16 to 56, Day 57 to 112, Day 113 to 168

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| End point values            | Ivacaftor       | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 34              | 35              |  |  |
| Units: Events               |                 |                 |  |  |
| Day 0 to 15                 | 3               | 1               |  |  |
| Day 16 to 56                | 4               | 2               |  |  |
| Day 57 to 112               | 2               | 6               |  |  |
| Day 113 to 168              | 1               | 4               |  |  |

**Statistical analyses**

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| Statistical analysis title              | Ivacaftor vs Placebo               |
| Comparison groups                       | Ivacaftor v Placebo                |
| Number of subjects included in analysis | 69                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| P-value                                 | = 0.8556                           |
| Method                                  | Cox Proportional Hazard Regression |

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**Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)**

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|                 |                                                                                |
|-----------------|--------------------------------------------------------------------------------|
| End point title | Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|--------------------------------------------------------------------------------|

End point description:

AE: any untoward medical occurrence, including clinically significant clinical laboratory assessments which occurs during course of study, whether it is considered related to study drug or not. SAE: medical event or condition, which falls into any of following categories, regardless of its relationship to the study drug: death, life threatening adverse experience, in-patient hospitalization/prolonged hospitalization,

persistent/significant disability/incapacity, congenital anomaly/birth defect, important medical event. Safety Set included all subjects who received at least 1 dose of study drug (ivacaftor or placebo).

|                                                                               |           |
|-------------------------------------------------------------------------------|-----------|
| End point type                                                                | Secondary |
| End point timeframe:                                                          |           |
| Baseline up to follow-up (3 to 4 weeks after last dose [last dose = Week 24]) |           |

| End point values            | Ivacaftor       | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 34              | 35              |  |  |
| Units: Subjects             |                 |                 |  |  |
| Subjects with any AEs       | 32              | 35              |  |  |
| Subjects with SAEs          | 4               | 6               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow-up (3 to 4 weeks after last dose [last dose = Week 24])

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Ivacaftor 150 mg tablet orally twice daily for 24 weeks.

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

Reporting group description:

Placebo-matched-to-ivacaftor tablet orally twice daily for 24 weeks.

| Serious adverse events                              | Ivacaftor       | Placebo         |  |
|-----------------------------------------------------|-----------------|-----------------|--|
| Total subjects affected by serious adverse events   |                 |                 |  |
| subjects affected / exposed                         | 4 / 34 (11.76%) | 6 / 35 (17.14%) |  |
| number of deaths (all causes)                       | 0               | 0               |  |
| number of deaths resulting from adverse events      |                 |                 |  |
| Gastrointestinal disorders                          |                 |                 |  |
| Constipation                                        |                 |                 |  |
| subjects affected / exposed                         | 1 / 34 (2.94%)  | 0 / 35 (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                         | 3 / 34 (8.82%)  | 6 / 35 (17.14%) |  |
| occurrences causally related to treatment / all     | 0 / 3           | 0 / 6           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Cellulitis                                          |                 |                 |  |
| subjects affected / exposed                         | 1 / 34 (2.94%)  | 0 / 35 (0.00%)  |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Ivacaftor        | Placebo           |  |
|-------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                  |                   |  |
| subjects affected / exposed                           | 32 / 34 (94.12%) | 35 / 35 (100.00%) |  |
| General disorders and administration site conditions  |                  |                   |  |
| Pyrexia                                               |                  |                   |  |
| subjects affected / exposed                           | 2 / 34 (5.88%)   | 6 / 35 (17.14%)   |  |
| occurrences (all)                                     | 3                | 9                 |  |
| Fatigue                                               |                  |                   |  |
| subjects affected / exposed                           | 2 / 34 (5.88%)   | 2 / 35 (5.71%)    |  |
| occurrences (all)                                     | 2                | 2                 |  |
| Influenza like illness                                |                  |                   |  |
| subjects affected / exposed                           | 2 / 34 (5.88%)   | 0 / 35 (0.00%)    |  |
| occurrences (all)                                     | 2                | 0                 |  |
| Pain                                                  |                  |                   |  |
| subjects affected / exposed                           | 0 / 34 (0.00%)   | 2 / 35 (5.71%)    |  |
| occurrences (all)                                     | 0                | 2                 |  |
| Chills                                                |                  |                   |  |
| subjects affected / exposed                           | 0 / 34 (0.00%)   | 1 / 35 (2.86%)    |  |
| occurrences (all)                                     | 0                | 1                 |  |
| Irritability                                          |                  |                   |  |
| subjects affected / exposed                           | 1 / 34 (2.94%)   | 0 / 35 (0.00%)    |  |
| occurrences (all)                                     | 1                | 0                 |  |
| Malaise                                               |                  |                   |  |
| subjects affected / exposed                           | 0 / 34 (0.00%)   | 1 / 35 (2.86%)    |  |
| occurrences (all)                                     | 0                | 1                 |  |
| Non-cardiac chest pain                                |                  |                   |  |
| subjects affected / exposed                           | 0 / 34 (0.00%)   | 1 / 35 (2.86%)    |  |
| occurrences (all)                                     | 0                | 1                 |  |
| Oedema peripheral                                     |                  |                   |  |
| subjects affected / exposed                           | 0 / 34 (0.00%)   | 1 / 35 (2.86%)    |  |
| occurrences (all)                                     | 0                | 1                 |  |
| Immune system disorders                               |                  |                   |  |

|                                                                        |                        |                       |  |
|------------------------------------------------------------------------|------------------------|-----------------------|--|
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 0 / 34 (0.00%)<br>0    | 2 / 35 (5.71%)<br>2   |  |
| Respiratory, thoracic and mediastinal disorders                        |                        |                       |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)              | 10 / 34 (29.41%)<br>14 | 9 / 35 (25.71%)<br>12 |  |
| Sputum increased<br>subjects affected / exposed<br>occurrences (all)   | 5 / 34 (14.71%)<br>6   | 4 / 35 (11.43%)<br>4  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)   | 5 / 34 (14.71%)<br>7   | 2 / 35 (5.71%)<br>3   |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 5 / 34 (14.71%)<br>5   | 2 / 35 (5.71%)<br>4   |  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 34 (0.00%)<br>0    | 6 / 35 (17.14%)<br>10 |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)        | 3 / 34 (8.82%)<br>4    | 3 / 35 (8.57%)<br>3   |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)           | 3 / 34 (8.82%)<br>3    | 2 / 35 (5.71%)<br>2   |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)           | 4 / 34 (11.76%)<br>4   | 1 / 35 (2.86%)<br>1   |  |
| Nasal oedema<br>subjects affected / exposed<br>occurrences (all)       | 1 / 34 (2.94%)<br>1    | 2 / 35 (5.71%)<br>2   |  |
| Rales<br>subjects affected / exposed<br>occurrences (all)              | 0 / 34 (0.00%)<br>0    | 3 / 35 (8.57%)<br>4   |  |
| Upper-airway cough syndrome                                            |                        |                       |  |

|                                |                |                |
|--------------------------------|----------------|----------------|
| subjects affected / exposed    | 3 / 34 (8.82%) | 0 / 35 (0.00%) |
| occurrences (all)              | 3              | 0              |
| Nasal mucosal disorder         |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all)              | 0              | 2              |
| Paranasal sinus hypersecretion |                |                |
| subjects affected / exposed    | 1 / 34 (2.94%) | 1 / 35 (2.86%) |
| occurrences (all)              | 1              | 1              |
| Sinus congestion               |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all)              | 0              | 2              |
| Asthma                         |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 2              |
| Bronchospasm                   |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 1              |
| Nasal turbinate abnormality    |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 1              |
| Pleural effusion               |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 1              |
| Pleurisy                       |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 1              |
| Pleuritic pain                 |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 1              |
| Respiration abnormal           |                |                |
| subjects affected / exposed    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)              | 0              | 1              |
| Respiratory tract congestion   |                |                |
| subjects affected / exposed    | 1 / 34 (2.94%) | 0 / 35 (0.00%) |
| occurrences (all)              | 1              | 0              |
| Tonsillolith                   |                |                |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Psychiatric disorders                            |                     |                     |  |
| Attention deficit/hyperactivity disorder         |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 2 / 35 (5.71%)<br>2 |  |
| Anxiety                                          |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Insomnia                                         |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Investigations                                   |                     |                     |  |
| Forced expiratory volume decreased               |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 3 / 34 (8.82%)<br>4 | 2 / 35 (5.71%)<br>3 |  |
| Blood potassium increased                        |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 2 / 35 (5.71%)<br>2 |  |
| C-reactive protein increased                     |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>2 | 1 / 35 (2.86%)<br>1 |  |
| Alanine aminotransferase increased               |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Blood bilirubin increased                        |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Blood calcium decreased                          |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1 |  |
| Blood creatine phosphokinase increased           |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>1 | 0 / 35 (0.00%)<br>0 |  |
| Blood pressure increased                         |                     |                     |  |

|                                                |                |                |  |
|------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Hepatic enzyme increased                       |                |                |  |
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Liver function test abnormal                   |                |                |  |
| subjects affected / exposed                    | 1 / 34 (2.94%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Platelet count increased                       |                |                |  |
| subjects affected / exposed                    | 1 / 34 (2.94%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Pulmonary function test decreased              |                |                |  |
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Urine leukocyte esterase positive              |                |                |  |
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| White blood cells urine positive               |                |                |  |
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Injury, poisoning and procedural complications |                |                |  |
| Laceration                                     |                |                |  |
| subjects affected / exposed                    | 1 / 34 (2.94%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 1              | 1              |  |
| Anal injury                                    |                |                |  |
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Animal bite                                    |                |                |  |
| subjects affected / exposed                    | 1 / 34 (2.94%) | 0 / 35 (0.00%) |  |
| occurrences (all)                              | 1              | 0              |  |
| Arthropod bite                                 |                |                |  |
| subjects affected / exposed                    | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Hand fracture                                  |                |                |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 34 (2.94%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Ligament sprain             |                 |                 |  |
| subjects affected / exposed | 1 / 34 (2.94%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Muscle strain               |                 |                 |  |
| subjects affected / exposed | 1 / 34 (2.94%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Periorbital haemorrhage     |                 |                 |  |
| subjects affected / exposed | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Tendon rupture              |                 |                 |  |
| subjects affected / exposed | 1 / 34 (2.94%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Thermal burn                |                 |                 |  |
| subjects affected / exposed | 1 / 34 (2.94%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)           | 1               | 0               |  |
| Nervous system disorders    |                 |                 |  |
| Headache                    |                 |                 |  |
| subjects affected / exposed | 6 / 34 (17.65%) | 5 / 35 (14.29%) |  |
| occurrences (all)           | 9               | 6               |  |
| Dizziness                   |                 |                 |  |
| subjects affected / exposed | 0 / 34 (0.00%)  | 2 / 35 (5.71%)  |  |
| occurrences (all)           | 0               | 3               |  |
| Lethargy                    |                 |                 |  |
| subjects affected / exposed | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Sciatica                    |                 |                 |  |
| subjects affected / exposed | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Sinus headache              |                 |                 |  |
| subjects affected / exposed | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)           | 0               | 1               |  |
| Ear and labyrinth disorders |                 |                 |  |
| Ear congestion              |                 |                 |  |

|                                  |                 |                 |  |
|----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed      | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                | 0               | 2               |  |
| Ear pain                         |                 |                 |  |
| subjects affected / exposed      | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Gastrointestinal disorders       |                 |                 |  |
| Diarrhoea                        |                 |                 |  |
| subjects affected / exposed      | 5 / 34 (14.71%) | 4 / 35 (11.43%) |  |
| occurrences (all)                | 6               | 4               |  |
| Vomiting                         |                 |                 |  |
| subjects affected / exposed      | 3 / 34 (8.82%)  | 4 / 35 (11.43%) |  |
| occurrences (all)                | 3               | 4               |  |
| Abdominal pain                   |                 |                 |  |
| subjects affected / exposed      | 4 / 34 (11.76%) | 0 / 35 (0.00%)  |  |
| occurrences (all)                | 5               | 0               |  |
| Abdominal pain upper             |                 |                 |  |
| subjects affected / exposed      | 2 / 34 (5.88%)  | 2 / 35 (5.71%)  |  |
| occurrences (all)                | 5               | 3               |  |
| Constipation                     |                 |                 |  |
| subjects affected / exposed      | 0 / 34 (0.00%)  | 3 / 35 (8.57%)  |  |
| occurrences (all)                | 0               | 3               |  |
| Abdominal discomfort             |                 |                 |  |
| subjects affected / exposed      | 2 / 34 (5.88%)  | 0 / 35 (0.00%)  |  |
| occurrences (all)                | 2               | 0               |  |
| Gastrooesophageal reflux disease |                 |                 |  |
| subjects affected / exposed      | 1 / 34 (2.94%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                | 1               | 1               |  |
| Nausea                           |                 |                 |  |
| subjects affected / exposed      | 1 / 34 (2.94%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                | 1               | 1               |  |
| Abdominal tenderness             |                 |                 |  |
| subjects affected / exposed      | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Loose tooth                      |                 |                 |  |
| subjects affected / exposed      | 0 / 34 (0.00%)  | 1 / 35 (2.86%)  |  |
| occurrences (all)                | 0               | 1               |  |

|                                                                                |                     |                      |  |
|--------------------------------------------------------------------------------|---------------------|----------------------|--|
| Palatal oedema<br>subjects affected / exposed<br>occurrences (all)             | 1 / 34 (2.94%)<br>1 | 0 / 35 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders                                         |                     |                      |  |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)         | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Drug eruption<br>subjects affected / exposed<br>occurrences (all)              | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Ingrowing nail<br>subjects affected / exposed<br>occurrences (all)             | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)       | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Rosacea<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 34 (2.94%)<br>1 | 0 / 35 (0.00%)<br>0  |  |
| Renal and urinary disorders                                                    |                     |                      |  |
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)            | 0 / 34 (0.00%)<br>0 | 1 / 35 (2.86%)<br>1  |  |
| Musculoskeletal and connective tissue disorders                                |                     |                      |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 34 (0.00%)<br>0 | 4 / 35 (11.43%)<br>4 |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 34 (2.94%)<br>1 | 2 / 35 (5.71%)<br>2  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 1 / 34 (2.94%)<br>1 | 1 / 35 (2.86%)<br>1  |  |

|                                                     |                  |                  |  |
|-----------------------------------------------------|------------------|------------------|--|
| Myalgia                                             |                  |                  |  |
| subjects affected / exposed                         | 1 / 34 (2.94%)   | 1 / 35 (2.86%)   |  |
| occurrences (all)                                   | 1                | 1                |  |
| Clubbing                                            |                  |                  |  |
| subjects affected / exposed                         | 0 / 34 (0.00%)   | 1 / 35 (2.86%)   |  |
| occurrences (all)                                   | 0                | 1                |  |
| Exostosis                                           |                  |                  |  |
| subjects affected / exposed                         | 1 / 34 (2.94%)   | 0 / 35 (0.00%)   |  |
| occurrences (all)                                   | 1                | 0                |  |
| Joint swelling                                      |                  |                  |  |
| subjects affected / exposed                         | 0 / 34 (0.00%)   | 1 / 35 (2.86%)   |  |
| occurrences (all)                                   | 0                | 1                |  |
| Neck pain                                           |                  |                  |  |
| subjects affected / exposed                         | 0 / 34 (0.00%)   | 1 / 35 (2.86%)   |  |
| occurrences (all)                                   | 0                | 1                |  |
| Infections and infestations                         |                  |                  |  |
| Infective pulmonary exacerbation of cystic fibrosis |                  |                  |  |
| subjects affected / exposed                         | 11 / 34 (32.35%) | 13 / 35 (37.14%) |  |
| occurrences (all)                                   | 14               | 18               |  |
| Upper respiratory tract infection                   |                  |                  |  |
| subjects affected / exposed                         | 3 / 34 (8.82%)   | 5 / 35 (14.29%)  |  |
| occurrences (all)                                   | 3                | 6                |  |
| Sinusitis                                           |                  |                  |  |
| subjects affected / exposed                         | 2 / 34 (5.88%)   | 5 / 35 (14.29%)  |  |
| occurrences (all)                                   | 4                | 6                |  |
| Bacterial disease carrier                           |                  |                  |  |
| subjects affected / exposed                         | 3 / 34 (8.82%)   | 1 / 35 (2.86%)   |  |
| occurrences (all)                                   | 6                | 1                |  |
| Influenza                                           |                  |                  |  |
| subjects affected / exposed                         | 1 / 34 (2.94%)   | 2 / 35 (5.71%)   |  |
| occurrences (all)                                   | 1                | 2                |  |
| Acute sinusitis                                     |                  |                  |  |
| subjects affected / exposed                         | 1 / 34 (2.94%)   | 1 / 35 (2.86%)   |  |
| occurrences (all)                                   | 1                | 1                |  |
| Viral upper respiratory tract infection             |                  |                  |  |

|                             |                |                |
|-----------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 35 (5.71%) |
| occurrences (all)           | 0              | 2              |
| Bronchitis                  |                |                |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Candidiasis                 |                |                |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Ear infection               |                |                |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) |
| occurrences (all)           | 2              | 0              |
| Folliculitis                |                |                |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Gastroenteritis             |                |                |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)           | 0              | 1              |
| Lip infection               |                |                |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)           | 0              | 1              |
| Nasopharyngitis             |                |                |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)           | 0              | 1              |
| Oral fungal infection       |                |                |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)           | 0              | 1              |
| Oral herpes                 |                |                |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 35 (0.00%) |
| occurrences (all)           | 1              | 0              |
| Otitis externa              |                |                |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)           | 0              | 1              |
| Otitis media                |                |                |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 35 (2.86%) |
| occurrences (all)           | 0              | 1              |
| Scarlet fever               |                |                |

|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed        | 1 / 34 (2.94%) | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Tonsillitis                        |                |                |  |
| subjects affected / exposed        | 1 / 34 (2.94%) | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Tooth abscess                      |                |                |  |
| subjects affected / exposed        | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Urinary tract infection            |                |                |  |
| subjects affected / exposed        | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Varicella                          |                |                |  |
| subjects affected / exposed        | 1 / 34 (2.94%) | 0 / 35 (0.00%) |  |
| occurrences (all)                  | 1              | 0              |  |
| Metabolism and nutrition disorders |                |                |  |
| Dehydration                        |                |                |  |
| subjects affected / exposed        | 0 / 34 (0.00%) | 2 / 35 (5.71%) |  |
| occurrences (all)                  | 0              | 2              |  |
| Decreased appetite                 |                |                |  |
| subjects affected / exposed        | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Hypoglycaemia                      |                |                |  |
| subjects affected / exposed        | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Hypokalaemia                       |                |                |  |
| subjects affected / exposed        | 0 / 34 (0.00%) | 1 / 35 (2.86%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Iron deficiency                    |                |                |  |
| subjects affected / exposed        | 1 / 34 (2.94%) | 0 / 35 (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    | An additional screening assessment of a comprehensive ophthalmologic examination was added for all subjects. Following feedback from Cystic Fibrosis Foundation Therapeutics, the number of electrocardiogram (ECG) assessments was reduced to shorten the duration of a study visit. -An inflammatory mediator assessment was added to the Follow-up Visit.                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 15 June 2012     | Abstinence was removed as a highly effective method of contraception for a subject's partner since this method would only be effective when practiced with a study subject who was also practicing abstinence.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 18 December 2012 | Collection of sweat chloride at Screening was required for subjects only if the value is not available in the subject's medical records and the value was needed for the diagnosis of CF to fulfill inclusion criterion. Changed the timing of when the Follow-up Visit was to occur after the last dose of study drug from "4 weeks ( $\pm$ 7 days)" to "3 to 4 weeks" in protocol -Ophthalmologic examinations were added as a safety endpoint for safety monitoring. Commercially available ivacaftor (Kalydeco™) was added to the list of prohibited medications. Clarified the statistical analysis was to be performed for the interim analysis. Requirement in protocol was changed to completing a case report form (CRF) for each subject screened in order to collect data for subjects who were screened but not enrolled. |
| 11 June 2013     | The exclusion of hypertonic saline use was removed. A recommendation was added that subjects should maintain their status of hypertonic saline use for the duration of the study and the final analysis was to be based on data from all enrolled subject assessments. Clarification was provided that, in the event of early study termination, subjects who had not had their Week 24 Visit were to be considered to have completed their assigned treatment duration.                                                                                                                                                                                                                                                                                                                                                              |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Enrollment was planned for a min of 40 & a max of approx. 80 subjects. Based upon power calculations & after exceeding min number of subjects defined in protocol, study was stopped by sponsor; however, the overall study status was completed.

Notes: