



Clinical trial results:

A Phase 3b, Open-Label Study to Evaluate Lumacaftor and Ivacaftor Combination Therapy in Subjects 12 Years and Older With Cystic Fibrosis and Advanced Lung Disease, Homozygous for the F508del-CFTR Mutation

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2017-001309-34 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 03 October 2016 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 10 August 2017 |
| First version publication date | 10 August 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX14-809-106 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02390219 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Vertex Pharmaceuticals Incorporated |
| Sponsor organisation address | 50 Northern Avenue, Boston, Massachusetts, United States, 022101862 |
| 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) | No |
| 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 | 20 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 October 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 October 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of lumacaftor/ivacaftor (LUM/IVA) combination therapy in subjects 12 years and older with cystic fibrosis (CF) and advanced lung disease and who are homozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 19 February 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 46 |
| Worldwide total number of subjects | 46 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 45 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 46 subjects were enrolled and treated in the study.

Period 1

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

Arms

| | |
|-----------|---------|
| Arm title | LUM/IVA |
|-----------|---------|

Arm description:

Subjects received LUM 400 milligram (mg) in combination with IVA 250 mg as fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.

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

Dosage and administration details:

LUM 400 mg in combination with IVA 250 mg as FDC tablet q12h for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet q12h was also permitted.

| Number of subjects in period 1 | LUM/IVA |
|--------------------------------|---------|
| Started | 46 |
| Completed | 33 |
| Not completed | 13 |
| Consent withdrawn by subject | 1 |
| Physician decision | 1 |
| Death | 1 |
| Adverse event | 6 |
| Unspecified | 2 |
| Lost to follow-up | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | LUM/IVA |
|-----------------------|---------|

Reporting group description:

Subjects received LUM 400 milligram (mg) in combination with IVA 250 mg as fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.

| Reporting group values | LUM/IVA | Total | |
|---|-------------|-------|--|
| Number of subjects | 46 | 46 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 32.1 ± 9 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 16 | 16 | |
| Male | 30 | 30 | |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | LUM/IVA |
| Reporting group description: Subjects received LUM 400 milligram (mg) in combination with IVA 250 mg as fixed-dose combination (FDC) tablet orally every 12 hours (q12h) for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted. | |

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

| | |
|--|---|
| End point title | Number of Subjects With Treatment Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs) ^[1] |
| End point description: AE: any untoward medical occurrence in a subject during the study; event does not necessarily have a causal relationship with treatment. This includes any newly occurring event/previous condition that has increased in severity/frequency after informed consent form is signed. AE includes serious as well as non-serious AEs. SAE (subset of AE): medical event, which falls into any of the following categories, regardless of its relationship to study drug: death, life threatening adverse experience, inpatient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event. TEAEs: AEs that started/ worsened on/after the start of study drug through the Safety Follow up Visit (4 weeks after the last dose of study drug). Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. Safety Set: all subjects who were exposed to any amount of study drug. | |
| End point type | Primary |
| End point timeframe: Day 1 up to Week 28 | |

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | LUM/IVA | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 46 | | | |
| Units: subjects | | | | |
| Subjects with AEs | 43 | | | |
| Subjects with SAEs | 18 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Up to Week 24

| | |
|---|--|
| End point title | Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Up to Week 24 |
| 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 12 to 17 years and for female subjects aged 12 to 15 years. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. Full Analysis Set (FAS) included all subjects who were enrolled and administered any amount of study drug. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Up to Week 24 | |

| End point values | LUM/IVA | | | |
|-------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: Percent predicted of FEV1 | | | | |
| least squares mean (standard error) | -0.4 (± 0.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) Up to Week 24

| | |
|-----------------|--|
| End point title | Absolute Change From Baseline in Forced Expiratory Volume in 1 Second (FEV1) Up to Week 24 |
|-----------------|--|

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 FEV1 (for age, gender, race, 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 12 to 17 years and for female subjects aged 12 to 15 years. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Up to Week 24 | |

| End point values | LUM/IVA | | | |
|-------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: Litre (L) | | | | |
| least squares mean (standard error) | -0.02 (± 0.03) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration For Which Subjects Received Intravenous (IV) Antibiotics

| | |
|-----------------|---|
| End point title | Duration For Which Subjects Received Intravenous (IV) Antibiotics |
|-----------------|---|

End point description:

The duration for which subjects received IV antibiotics for sinopulmonary signs and symptoms were reported. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here "Number of subjects analyzed" signifies those subjects who received at least one IV antibiotic for sinopulmonary signs and symptoms.

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

End point timeframe:

Baseline through Week 24

| End point values | LUM/IVA | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 22 | | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 11.38 (± 18.15) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospitalizations

| | |
|-----------------|----------------------------|
| End point title | Number of Hospitalizations |
|-----------------|----------------------------|

End point description:

Number of hospitalizations (all causes) through Week 24 was summarized. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here "Number of subjects analyzed" analyzed signifies those subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline through Week 24

| End point values | LUM/IVA | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: hospitalizations | | | | |
| number (not applicable) | 23 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Sweat Chloride at Average of Day 15 and Week 4

| | |
|-----------------|---|
| End point title | Absolute Change From Baseline in Sweat Chloride at Average of Day 15 and Week 4 |
|-----------------|---|

End point description:

Sweat samples were collected using an approved collection device. Baseline was defined as the average of the measurements at screening and on Day 1 pre-dose. The average absolute change from baseline in sweat chloride was derived as: (Average of Day 15 and Week 4 value) minus Baseline value. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here "Number of subjects analyzed" analyzed signifies those subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Day 15 and Week 4

| End point values | LUM/IVA | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 41 | | | |
| Units: Millimoles per litre (mmol/L) | | | | |
| least squares mean (standard error) | -16.4 (± 1.3) | | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Absolute 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), the scaled score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. Results were reported as planned, as a combined single LUM/IVA arm irrespective of permitted dose modification. FAS included all subjects who were enrolled and administered any amount of study drug. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline, Through Week 24

| | | | | |
|-------------------------------------|------------------|--|--|--|
| End point values | LUM/IVA | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 44 | | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 2.5 (\pm 1.7) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 28

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

Dictionary used

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

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|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | LUM/IVA |
|-----------------------|---------|

Reporting group description:

Subjects received LUM 400 mg in combination with IVA 250 mg as FDC tablet orally q12h for 24 weeks. A reduced initial dose of LUM 200 mg in combination with IVA 125 mg FDC tablet orally q12h was permitted.

| Serious adverse events | LUM/IVA | | |
|--|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 46 (39.13%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiration abnormal | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 16 / 46 (34.78%) | | |
| occurrences causally related to treatment / all | 2 / 27 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | LUM/IVA | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 43 / 46 (93.48%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | | |
| occurrences (all) | 8 | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | | |
| occurrences (all) | 5 | | |
| Pain | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 3 | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 4 | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiration abnormal | | | |
| subjects affected / exposed | 25 / 46 (54.35%) | | |
| occurrences (all) | 39 | | |
| Cough | | | |
| subjects affected / exposed | 21 / 46 (45.65%) | | |
| occurrences (all) | 32 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 20 / 46 (43.48%) | | |
| occurrences (all) | 28 | | |
| Sputum increased | | | |
| subjects affected / exposed | 13 / 46 (28.26%) | | |
| occurrences (all) | 18 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 9 / 46 (19.57%) | | |
| occurrences (all) | 9 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | | |
| occurrences (all) | 10 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | | |
| occurrences (all) | 6 | | |
| Wheezing | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | | |
| occurrences (all) | 7 | | |
| Respiratory tract congestion | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 4 | | |
| Upper respiratory tract congestion | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 3 | | |
| Productive cough | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 3 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Increased viscosity of bronchial secretion | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Lower respiratory tract congestion | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Painful respiration | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Paranasal sinus hypersecretion | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|---------------------|--|--|
| Sinus congestion subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 2 | | |
| Sputum retention subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Upper-airway cough syndrome subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 46 (8.70%) 4 | | |
| Affect lability subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Depression subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Irritability subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Pulmonary function test decreased subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Blood glucose increased | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Blood immunoglobulin E increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Blood pressure diastolic increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Fungal test positive | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Oxygen consumption increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Prostatic specific antigen increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Sputum abnormal | | | |

| | | | |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 2 | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 46 (15.22%) | | |
| occurrences (all) | 9 | | |
| Lethargy | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | | |
| occurrences (all) | 5 | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 3 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |

| | | | |
|--|----------------------|--|--|
| Lacrimation increased subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 5 / 46 (10.87%) 7 | | |
| Nausea subjects affected / exposed occurrences (all) | 5 / 46 (10.87%) 5 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Flatulence subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Dysphagia subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Gastrointestinal tract mucosal discolouration subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Gastrooesophageal reflux disease | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 3 | | |
| Rash | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 3 | | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Acne | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Rash macular | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|------------------|--|--|
| Renal and urinary disorders | | | |
| Nephrocalcinosis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 20 / 46 (43.48%) | | |
| occurrences (all) | 26 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 3 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 3 | | |

| | | | |
|------------------------------------|----------------|--|--|
| Chronic sinusitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Labyrinthitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Sinusitis bacterial | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 5 / 46 (10.87%) | | |
| occurrences (all) | 5 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 26 January 2015 | 1. Modified eligibility criteria; 2. The Patient Health Questionnaire (PHQ) was changed from PHQ-9 to PHQ-8. |
| 29 April 2015 | 1. Included additional safety precautions; 2. Text was added to reflect the option for dose modification |
| 14 July 2015 | 1. Clarified that enrollment was no longer limited to subjects with ppFEV1 values greater than or equal to (\geq) 30 to less than ($<$) 40 at Screening and \geq 30 on Day 1. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported