

**Clinical trial results:****A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)****Summary**

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2018-000183-28 |
| Trial protocol | SE DE GB CZ BE NL AT GR FR IT |
| Global end of trial date | 24 April 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 20 November 2019 |
| First version publication date | 20 November 2019 |

Trial information**Trial identification**

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX17-445-102 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03525444 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Vertex Pharmaceuticals Incorporated |
| Sponsor organisation address | 50 Northern Avenue, Boston, Massachusetts, United States, |
| 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-002324-PIP01-17 |
| 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 | 14 May 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 April 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 April 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for the F508del and a minimal function mutation (F/MF subjects).

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 | 15 June 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 24 |
| Country: Number of subjects enrolled | Italy: 22 |
| Country: Number of subjects enrolled | United States: 216 |
| Country: Number of subjects enrolled | Australia: 24 |
| Country: Number of subjects enrolled | Netherlands: 19 |
| Country: Number of subjects enrolled | Sweden: 4 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Austria: 13 |
| Country: Number of subjects enrolled | Belgium: 18 |
| Country: Number of subjects enrolled | Czech Republic: 6 |
| Country: Number of subjects enrolled | France: 20 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Greece: 3 |
| Worldwide total number of subjects | 405 |
| EEA total number of subjects | 141 |

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) | 116 |
| Adults (18-64 years) | 289 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in subjects with cystic fibrosis (CF) aged 12 years or older.

Period 1

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

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

| | |
|--|-------------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo (matched to VX-445/TEZ/IVA) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to VX-445/TEZ/IVA once daily in the morning.

| | |
|--|--------------------------|
| Investigational medicinal product name | Placebo (matched to IVA) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to IVA once daily in the evening.

| | |
|------------------|-------------------|
| Arm title | VX-445/TEZ/IVA TC |
|------------------|-------------------|

Arm description:

Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | VX-445/TEZ/IVA |
| Investigational medicinal product code | VX-445/VX-661/VX-770 |
| Other name | VX-445/Tezacaftor/Ivacaftor fixed dose combination |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-445/TEZ/IVA once daily in the morning.

| | |
|--|-----------|
| Investigational medicinal product name | IVA |
| Investigational medicinal product code | VX-770 |
| Other name | Ivacaftor |
| Pharmaceutical forms | Tablet |

Dosage and administration details:

Subjects received IVA once daily in the evening.

| Number of subjects in period 1^[1] | Placebo | VX-445/TEZ/IVA TC |
|---|---------|-------------------|
| Started | 203 | 200 |
| Completed | 203 | 197 |
| Not completed | 0 | 3 |
| Other | - | 1 |
| Adverse event | - | 1 |
| Withdrawal of consent (not due to AE) | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In the above disposition summary, data are presented for 403 subjects who were randomized and dosed in the TC treatment period. Two subjects were enrolled in to the study and randomized but were not dosed in the TC treatment period. Therefore, the total number of enrolled subjects is 405 but the number of subjects reported in subject disposition and baseline is 403.

Baseline characteristics

Reporting groups

| | |
|--|-------------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period. | |
| Reporting group title | VX-445/TEZ/IVA TC |
| Reporting group description: Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period. | |

| Reporting group values | Placebo | VX-445/TEZ/IVA TC | Total |
|---|----------------|-------------------|-------|
| Number of subjects | 203 | 200 | 403 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 26.8 ± 11.3 | 25.6 ± 9.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 98 | 96 | 194 |
| Male | 105 | 104 | 209 |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period. | |
| Reporting group title | VX-445/TEZ/IVA TC |
| Reporting group description: | |
| Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period. | |

Primary: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

| | |
|-------------------------------|--|
| End point title | Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline through Week 24 | |

| End point values | Placebo | VX-445/TEZ/IVA TC | | |
|-------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203 | 200 | | |
| Units: percentage points | | | | |
| least squares mean (standard error) | -0.4 (\pm 0.5) | 13.9 (\pm 0.6) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis |
| Comparison groups | VX-445/TEZ/IVA TC v Placebo |
| Number of subjects included in analysis | 403 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 14.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.7 |
| upper limit | 15.8 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug in TC treatment period up to 28 days after last dose of study drug or to the completion of study participation date, whichever occurs first

Adverse event reporting additional description:

Adverse events are presented as per Safety Set. Treatment assignments for subjects in the Safety Set are based on actual treatment received, such that all subjects who received at least 1 dose of VX-445/TEZ/IVA TC were included in the VX-445/TEZ/IVA TC group for the safety analysis, even if they were assigned to the placebo group.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

| | |
|-----------------------|-------------------|
| Reporting group title | VX-445/TEZ/IVA TC |
|-----------------------|-------------------|

Reporting group description:

Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

| Serious adverse events | Placebo | VX-445/TEZ/IVA TC | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 42 / 201 (20.90%) | 28 / 202 (13.86%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Axonal neuropathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental impairment | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroglycopenia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site inflammation | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Distal intestinal obstruction syndrome | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 201 (1.49%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diaphragmatic paralysis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Painful respiration | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder enlargement | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal hypertension | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 2 / 202 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity vasculitis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|--|-------------------|------------------|--|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 33 / 201 (16.42%) | 11 / 202 (5.45%) | |
| occurrences causally related to treatment / all | 0 / 44 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 3 / 202 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical mycobacterial lower respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coccidioidomycosis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital herpes simplex | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 201 (0.00%) | 1 / 202 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral sinusitis | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 201 (0.50%) | 0 / 202 (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: 5 %

| Non-serious adverse events | Placebo | VX-445/TEZ/IVA TC | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 180 / 201 (89.55%) | 168 / 202 (83.17%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 7 / 201 (3.48%) | 20 / 202 (9.90%) | |
| occurrences (all) | 8 | 22 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 9 / 201 (4.48%) | 19 / 202 (9.41%) | |
| occurrences (all) | 9 | 20 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 201 (1.99%) | 19 / 202 (9.41%) | |
| occurrences (all) | 4 | 21 | |
| Bacterial test positive | | | |
| subjects affected / exposed | 10 / 201 (4.98%) | 5 / 202 (2.48%) | |
| occurrences (all) | 13 | 5 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 201 (1.00%) | 10 / 202 (4.95%) | |
| occurrences (all) | 2 | 11 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 30 / 201 (14.93%) | 35 / 202 (17.33%) | |
| occurrences (all) | 42 | 49 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 19 / 201 (9.45%) | 17 / 202 (8.42%) | |
| occurrences (all) | 25 | 18 | |
| Fatigue | | | |
| subjects affected / exposed | 20 / 201 (9.95%) | 9 / 202 (4.46%) | |
| occurrences (all) | 22 | 9 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | |
|---|-------------------|-------------------|
| subjects affected / exposed | 14 / 201 (6.97%) | 26 / 202 (12.87%) |
| occurrences (all) | 23 | 32 |
| Abdominal pain | | |
| subjects affected / exposed | 12 / 201 (5.97%) | 20 / 202 (9.90%) |
| occurrences (all) | 20 | 24 |
| Nausea | | |
| subjects affected / exposed | 14 / 201 (6.97%) | 16 / 202 (7.92%) |
| occurrences (all) | 17 | 16 |
| Vomiting | | |
| subjects affected / exposed | 10 / 201 (4.98%) | 12 / 202 (5.94%) |
| occurrences (all) | 13 | 14 |
| Constipation | | |
| subjects affected / exposed | 12 / 201 (5.97%) | 6 / 202 (2.97%) |
| occurrences (all) | 12 | 6 |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough | | |
| subjects affected / exposed | 77 / 201 (38.31%) | 34 / 202 (16.83%) |
| occurrences (all) | 113 | 39 |
| Sputum increased | | |
| subjects affected / exposed | 39 / 201 (19.40%) | 40 / 202 (19.80%) |
| occurrences (all) | 47 | 47 |
| Oropharyngeal pain | | |
| subjects affected / exposed | 25 / 201 (12.44%) | 20 / 202 (9.90%) |
| occurrences (all) | 26 | 27 |
| Haemoptysis | | |
| subjects affected / exposed | 27 / 201 (13.43%) | 9 / 202 (4.46%) |
| occurrences (all) | 39 | 10 |
| Nasal congestion | | |
| subjects affected / exposed | 15 / 201 (7.46%) | 19 / 202 (9.41%) |
| occurrences (all) | 18 | 21 |
| Productive cough | | |
| subjects affected / exposed | 16 / 201 (7.96%) | 12 / 202 (5.94%) |
| occurrences (all) | 17 | 12 |
| Rhinorrhoea | | |

| | | | |
|---|--------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 201 (2.99%) 7 | 17 / 202 (8.42%) 19 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 13 / 201 (6.47%) 15 | 5 / 202 (2.48%) 5 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 9 / 201 (4.48%) 11 | 17 / 202 (8.42%) 20 | |
| Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all) | 83 / 201 (41.29%) 137 | 41 / 202 (20.30%) 53 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 26 / 201 (12.94%) 34 | 22 / 202 (10.89%) 30 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 22 / 201 (10.95%) 26 | 24 / 202 (11.88%) 30 | |
| Rhinitis subjects affected / exposed occurrences (all) | 11 / 201 (5.47%) 14 | 15 / 202 (7.43%) 18 | |
| Sinusitis subjects affected / exposed occurrences (all) | 8 / 201 (3.98%) 8 | 11 / 202 (5.45%) 15 | |
| Influenza subjects affected / exposed occurrences (all) | 3 / 201 (1.49%) 3 | 12 / 202 (5.94%) 13 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 13 April 2018 | Updated study drug regimen, dosing guidance, dose and population rationale |
| 19 July 2018 | Revised exclusion criteria |
| 30 October 2018 | A European-specific version of the protocol was created with a 24-week primary endpoint |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported