



Clinical trial results:

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-659 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2016-003585-11 |
| Trial protocol | IE GB |
| Global end of trial date | 28 February 2018 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 16 July 2021 |
| First version publication date | 16 March 2019 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Secondary endpoints results need to be added |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | VX16-659-101 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03224351 |
| 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, +1 877 634 8789, medicalinfo@vrtx.com |
| Scientific contact | Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 877 634 8789, 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? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 28 March 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and efficacy of VX-659 in triple combination (TC) with Tezacaftor/Ivacaftor (TEZ/IVA) or with TEZ/VX-561.

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 | 08 August 2017 |
| 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 | United Kingdom: 29 |
| Country: Number of subjects enrolled | Ireland: 11 |
| Country: Number of subjects enrolled | United States: 77 |
| Country: Number of subjects enrolled | Israel: 7 |
| Worldwide total number of subjects | 124 |
| EEA total number of subjects | 40 |

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) | 0 |
| Adults (18-64 years) | 124 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included 3 parts and was conducted in adult subjects with cystic fibrosis (CF).

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, Assessor |

Arms

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

| | |
|------------------|-----------------|
| Arm title | Part 1: Placebo |
|------------------|-----------------|

Arm description:

Subjects received placebo matched to VX-659/TEZ/IVA in TC treatment period for 4 weeks and placebo matched to TEZ/IVA in washout period for 4 days.

| | |
|--|-----------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo (matched to VX-659) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to VX-659 once daily.

| | |
|--|------------------------------|
| Investigational medicinal product name | Placebo (matched to 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 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 | Part 1: VX-659/TEZ/IVA TC - Low Dose |
|------------------|--------------------------------------|

Arm description:

Subjects received VX-659 80 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------|
| Investigational medicinal product name | VX-659 |
| Investigational medicinal product code | VX-659 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-659 low dose once daily.

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

Dosage and administration details:

Subjects received TEZ/IVA once daily in the morning.

| | |
|--|-----------|
| Investigational medicinal product name | IVA |
| Investigational medicinal product code | VX-770 |
| Other name | Ivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received IVA once daily in the evening.

| | |
|------------------|---|
| Arm title | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
|------------------|---|

Arm description:

Subjects received VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks
and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | VX-659 |
| Investigational medicinal product code | VX-659 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-659 medium dose once daily.

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

Dosage and administration details:

Subjects received TEZ/IVA once daily in the morning.

| | |
|--|-----------|
| Investigational medicinal product name | IVA |
| Investigational medicinal product code | VX-770 |
| Other name | Ivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received IVA once daily in the evening.

| | |
|------------------|---------------------------------------|
| Arm title | Part 1: VX-659/TEZ/IVA TC - High Dose |
|------------------|---------------------------------------|

Arm description:

Subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks

and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | VX-659 |
| Investigational medicinal product code | VX-659 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-659 high dose once daily.

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

Dosage and administration details:

Subjects received TEZ/IVA once daily in the morning.

| | |
|--|-----------|
| Investigational medicinal product name | IVA |
| Investigational medicinal product code | VX-770 |
| Other name | Ivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received IVA once daily in the evening.

| | |
|------------------|-----------------|
| Arm title | Part 2: TEZ/IVA |
|------------------|-----------------|

Arm description:

Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks.

| | |
|--|-----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo (matched to VX-659) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to VX-659 once daily.

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

Dosage and administration details:

Subjects received TEZ/IVA once daily in the morning.

| | |
|--|-----------|
| Investigational medicinal product name | IVA |
| Investigational medicinal product code | VX-770 |
| Other name | Ivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received IVA once daily in the evening.

| | |
|--|---|
| Arm title | Part 2: VX-659/TEZ/IVA TC |
| Arm description: Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | VX-659 |
| Investigational medicinal product code | VX-659 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Subjects received VX-659 once daily. | |
| Investigational medicinal product name | TEZ/IVA |
| Investigational medicinal product code | VX-661/VX-770 |
| Other name | Tezacaftor/Ivacaftor fixed dose combination |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Subjects received TEZ/IVA once daily in the morning. | |
| Investigational medicinal product name | IVA |
| Investigational medicinal product code | VX-770 |
| Other name | Ivacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Subjects received IVA once daily in the evening. | |
| Arm title | Part 3: Placebo |
| Arm description: Subjects received placebo matched to VX-659/TEZ/VX-561 in TC treatment period for 4 weeks. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo (matched to VX-659) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Subjects received placebo matched to VX-659 once daily. | |
| Investigational medicinal product name | Placebo (matched to TEZ) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Subjects received placebo matched to TEZ once daily. | |
| Investigational medicinal product name | Placebo (matched to VX-561) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Subjects received placebo matched to VX-561 once daily.

| | |
|------------------|------------------------------|
| Arm title | Part 3: VX-659/TEZ/VX-561 TC |
|------------------|------------------------------|

Arm description:

Subjects received VX-659 400 mg qd/TEZ 100 mg qd/VX-561 200 mg qd in TC treatment period for 4 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | VX-659 |
| Investigational medicinal product code | VX-659 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-659 once daily.

| | |
|--|------------|
| Investigational medicinal product name | TEZ |
| Investigational medicinal product code | VX-661 |
| Other name | Tezacaftor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received TEZ once daily.

| | |
|--|----------|
| Investigational medicinal product name | VX-561 |
| Investigational medicinal product code | VX-561 |
| Other name | CTP-656 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-561 once daily.

| Number of subjects in period 1 ^[1] | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
|---|-----------------|--------------------------------------|---|
| | | | |
| Started | 10 | 11 | 20 |
| Completed | 10 | 11 | 20 |

| Number of subjects in period 1 ^[1] | Part 1: VX-659/TEZ/IVA TC - High Dose | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC |
|---|---------------------------------------|-----------------|---------------------------|
| | | | |
| Started | 22 | 11 | 18 |
| Completed | 22 | 11 | 18 |

| Number of subjects in period 1 ^[1] | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC |
|---|-----------------|------------------------------|
| | | |
| Started | 6 | 19 |

| | | |
|-----------|---|----|
| Completed | 6 | 19 |
|-----------|---|----|

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: There were 117 subjects dosed in the TC treatment period for all 3 parts. 7 subjects were dosed in the run-in period in part 2 but were not dosed in TC treatment period. Therefore, the total enrolled subjects are 124 where as the subjects reported in disposition and baseline are 117.

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Part 1: Placebo |
| Reporting group description: Subjects received placebo matched to VX-659/TEZ/IVA in TC treatment period for 4 weeks and placebo matched to TEZ/IVA in washout period for 4 days. | |
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - Low Dose |
| Reporting group description: Subjects received VX-659 80 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days. | |
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
| Reporting group description: Subjects received VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days. | |
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - High Dose |
| Reporting group description: Subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days. | |
| Reporting group title | Part 2: TEZ/IVA |
| Reporting group description: Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks. | |
| Reporting group title | Part 2: VX-659/TEZ/IVA TC |
| Reporting group description: Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks. | |
| Reporting group title | Part 3: Placebo |
| Reporting group description: Subjects received placebo matched to VX-659/TEZ/VX-561 in TC treatment period for 4 weeks. | |
| Reporting group title | Part 3: VX-659/TEZ/VX-561 TC |
| Reporting group description: Subjects received VX-659 400 mg qd/TEZ 100 mg qd/VX-561 200 mg qd in TC treatment period for 4 weeks. | |

| Reporting group values | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
|------------------------|-----------------|--------------------------------------|---|
| Number of subjects | 10 | 11 | 20 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---------------|----------------|---------------|
| Age continuous Units: years arithmetic mean standard deviation | 26.6 ± 6.0 | 32.0 ± 11.7 | 31.4 ± 9.7 |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 7 | 7 |
| Male | 6 | 4 | 13 |
| Ethnicity (NIH/ OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 2 |
| Not Hispanic or Latino | 10 | 11 | 18 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 10 | 11 | 20 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) | | | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | | | |
| Units: Subjects | | | |
| <40 percent | 2 | 0 | 1 |
| ≥40 to <70 percent | 6 | 9 | 13 |
| ≥70 to ≤90 percent | 2 | 2 | 6 |
| >90 percent | 0 | 0 | 0 |

| Reporting group values | Part 1: VX-659/TEZ/IVA TC - High Dose | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC |
|------------------------------------|---------------------------------------|-----------------|---------------------------|
| Number of subjects | 22 | 11 | 18 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|---------------|
| Age continuous Units: years arithmetic mean standard deviation | 27.2 ± 6.6 | 32.5 ± 7.5 | 33.4 ± 9.2 |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 4 | 6 |
| Male | 10 | 7 | 12 |
| Ethnicity (NIH/ OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 1 |
| Not Hispanic or Latino | 22 | 10 | 17 |
| Unknown or Not Reported | 0 | 0 | 0 |

| | | | |
|---|----|----|----|
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 22 | 11 | 16 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 1 |
| Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) | | | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | | | |
| Units: Subjects | | | |
| <40 percent | 2 | 0 | 1 |
| >=40 to <70 percent | 13 | 8 | 12 |
| >=70 to <=90 percent | 7 | 3 | 5 |
| >90 percent | 0 | 0 | 0 |

| Reporting group values | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC | Total |
|------------------------|-----------------|------------------------------|-------|
| Number of subjects | 6 | 19 | 117 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-------|-------|-----|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 24.5 | 32.5 | |
| standard deviation | ± 5.3 | ± 9.4 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 11 | 54 |
| Male | 3 | 8 | 63 |
| Ethnicity (NIH/ OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | 6 |
| Not Hispanic or Latino | 5 | 18 | 111 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 2 | 2 |
| White | 6 | 17 | 113 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 1 |
| Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) | | | |
| FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. | | | |
| Units: Subjects | | | |

| | | | |
|----------------------|---|----|----|
| <40 percent | 0 | 2 | 8 |
| >=40 to <70 percent | 5 | 13 | 79 |
| >=70 to <=90 percent | 1 | 4 | 30 |
| >90 percent | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Part 1: Placebo |
| Reporting group description: Subjects received placebo matched to VX-659/TEZ/IVA in TC treatment period for 4 weeks and placebo matched to TEZ/IVA in washout period for 4 days. | |
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - Low Dose |
| Reporting group description: Subjects received VX-659 80 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days. | |
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
| Reporting group description: Subjects received VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days. | |
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - High Dose |
| Reporting group description: Subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days. | |
| Reporting group title | Part 2: TEZ/IVA |
| Reporting group description: Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks. | |
| Reporting group title | Part 2: VX-659/TEZ/IVA TC |
| Reporting group description: Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks. | |
| Reporting group title | Part 3: Placebo |
| Reporting group description: Subjects received placebo matched to VX-659/TEZ/VX-561 in TC treatment period for 4 weeks. | |
| Reporting group title | Part 3: VX-659/TEZ/VX-561 TC |
| Reporting group description: Subjects received VX-659 400 mg qd/TEZ 100 mg qd/VX-561 200 mg qd in TC treatment period for 4 weeks. | |

Primary: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

| | |
|---|---|
| End point title | Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) ^[1] |
| End point description: Safety Set included all subjects who received at least 1 dose of study drug in TC treatment period. | |
| End point type | Primary |

End point timeframe:

Day 1 Through Safety Follow-up (up to Day 61 for Part 1, Day 85 for Part 2 and Day 57 for Part 3)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for primary safety endpoint.

| End point values | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose | Part 1: VX-659/TEZ/IVA TC - High Dose |
|-----------------------------|-----------------|--------------------------------------|---|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 11 | 20 | 22 |
| Units: subjects | | | | |
| Subjects with TEAEs | 9 | 10 | 15 | 17 |
| Subjects with SAEs | 3 | 1 | 4 | 1 |

| End point values | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC |
|-----------------------------|-----------------|---------------------------|-----------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 18 | 6 | 19 |
| Units: subjects | | | | |
| Subjects with TEAEs | 9 | 15 | 6 | 18 |
| Subjects with SAEs | 2 | 1 | 3 | 2 |

Statistical analyses

No statistical analyses for this end point

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) ^[2] |
|-----------------|---|

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Full Analysis Set (FAS) included all randomized subjects with an eligible cystic fibrosis transmembrane conductance regulator protein (CFTR) genotype and received at least 1 dose of study drug.

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

End point timeframe:

From Baseline Through Day 29

Notes:

[2] - 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: The study is not designed to perform between treatment group comparisons.

| End point values | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose | Part 1: VX-659/TEZ/IVA TC - High Dose |
|--|-------------------|--------------------------------------|---|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 11 | 20 | 22 |
| Units: percentage points | | | | |
| least squares mean (confidence interval 95%) | 0.4 (-5.3 to 6.1) | 10.2 (4.8 to 15.5) | 12.0 (8.0 to 16.0) | 13.3 (9.5 to 17.1) |

| End point values | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC |
|--|-------------------|---------------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 18 | 6 | 19 |
| Units: percentage points | | | | |
| least squares mean (confidence interval 95%) | 0.0 (-3.9 to 3.9) | 9.7 (6.6 to 12.7) | -5.0 (-12.2 to 2.1) | 12.2 (8.3 to 16.2) |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Sweat Chloride Concentrations

| | |
|------------------------|--|
| End point title | Absolute Change in Sweat Chloride Concentrations |
| End point description: | Sweat samples were collected using an approved collection device. FAS. |
| End point type | Secondary |
| End point timeframe: | From Baseline Through Day 29 |

| End point values | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose | Part 1: VX-659/TEZ/IVA TC - High Dose |
|--|--------------------|--------------------------------------|---|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 11 | 20 | 22 |
| Units: millimole per liter (mmol/L) | | | | |
| least squares mean (confidence interval 95%) | 2.9 (-6.3 to 12.2) | -45.7 (-54.4 to -37.0) | -43.8 (-50.7 to -37.0) | -51.4 (-57.8 to -44.9) |

| End point values | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC |
|------------------|-----------------|---------------------------|-----------------|------------------------------|
|------------------|-----------------|---------------------------|-----------------|------------------------------|

| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
|--|-------------------|------------------------|---------------------|------------------------|
| Number of subjects analysed | 11 | 18 | 6 | 19 |
| Units: millimole per liter (mmol/L) | | | | |
| least squares mean (confidence interval 95%) | 3.0 (-2.8 to 8.9) | -42.2 (-46.8 to -37.7) | -1.3 (-12.4 to 9.8) | -38.1 (-44.4 to -31.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change in ppFEV1

| | |
|--|---------------------------|
| End point title | Relative Change in ppFEV1 |
| End point description: FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. FAS. | |
| End point type | Secondary |
| End point timeframe: From Baseline Through Day 29 | |

| End point values | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose | Part 1: VX-659/TEZ/IVA TC - High Dose |
|--|---------------------|--------------------------------------|---|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 11 | 20 | 22 |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | 0.0 (-10.5 to 10.4) | 18.8 (8.9 to 28.7) | 21.1 (13.8 to 28.5) | 24.6 (17.6 to 31.6) |

| End point values | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC |
|--|-------------------|---------------------------|----------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 18 | 6 | 19 |
| Units: percent change | | | | |
| least squares mean (confidence interval 95%) | 0.1 (-7.1 to 7.3) | 17.3 (11.7 to 23.0) | -11.3 (-23.7 to 1.1) | 21.5 (14.6 to 28.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score

| | |
|-----------------|--|
| End point title | Absolute Change in Cystic Fibrosis Questionnaire-Revised |
|-----------------|--|

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, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. FAS.

End point type

Secondary

End point timeframe:

From Baseline at Day 29

| End point values | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose | Part 1: VX-659/TEZ/IVA TC - High Dose |
|--|--------------------|--------------------------------------|---|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 11 | 20 | 22 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | 4.7 (-7.5 to 16.8) | 24.6 (13.0 to 36.2) | 19.8 (11.0 to 28.6) | 21.8 (13.6 to 30.0) |

| End point values | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC |
|--|--------------------|---------------------------|---------------------|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 18 | 6 | 19 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | 2.9 (-5.2 to 11.1) | 19.5 (13.1 to 25.9) | -4.1 (-17.8 to 9.6) | 14.7 (7.1 to 22.4) |

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Pre-dose Concentration (Ctough) of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561

End point title

Observed Pre-dose Concentration (Ctough) of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561^[3]

End point description:

Pharmacokinetic Set (PK) included all subjects who have received at least 1 dose of study drug in TC treatment period. Here "n" signifies those subjects who were evaluable at specified time points and "99999" represents "not applicable" for particular category for Ctough assessments. VX-659 category was not applicable for Part 2: TEZ/IVA group. VX-561 category was applicable for Part 3: TC group only. IVA and M1-IVA categories were not applicable for Part 3: TC group.

End point type

Secondary

End point timeframe:

Pre-dose at Day 15 and Day 29

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Parts 1 and 3: Placebo arms were not applicable for this endpoint.

| End point values | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose | Part 1: VX-659/TEZ/IVA TC - High Dose | Part 2: TEZ/IVA |
|---|--------------------------------------|---|---------------------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 20 | 22 | 11 |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| VX-659: Day 15 (n=10, 16, 19, 0, 17, 17) | 393 (± 604) | 622 (± 429) | 1100 (± 731) | 99999 (± 99999) |
| VX-659: Day 29 (n=11, 19, 22, 0, 18, 19) | 566 (± 861) | 699 (± 489) | 1080 (± 582) | 99999 (± 99999) |
| TEZ: Day 15 (n=10, 16, 19, 7, 17, 17) | 1910 (± 1360) | 1250 (± 907) | 1110 (± 455) | 1050 (± 473) |
| TEZ: Day 29 (n=11, 19, 22, 11, 18, 19) | 1910 (± 1230) | 1050 (± 553) | 1010 (± 479) | 1150 (± 480) |
| M1-TEZ: Day 15 (n=10, 16, 19, 7, 17, 19) | 4390 (± 949) | 3710 (± 1230) | 4280 (± 1190) | 4160 (± 1260) |
| M1-TEZ: Day 29 (n=11, 19, 22, 11, 18, 19) | 4300 (± 774) | 3650 (± 1280) | 3870 (± 1020) | 3790 (± 1080) |
| IVA: Day 15 (n=10, 16, 19, 7, 17, 0) | 824 (± 781) | 522 (± 567) | 423 (± 261) | 458 (± 239) |
| IVA: Day 29 (n=11, 19, 22, 11, 18, 0) | 719 (± 604) | 443 (± 398) | 371 (± 220) | 490 (± 179) |
| M1-IVA: Day 15 (n=10, 16, 19, 7, 17, 0) | 1200 (± 711) | 1050 (± 852) | 1170 (± 674) | 1310 (± 684) |
| M1-IVA Day 29 (n=11, 19, 22, 11, 18, 0) | 1130 (± 682) | 1140 (± 950) | 1030 (± 460) | 1240 (± 321) |
| VX-561: Day 15 (n=0, 0, 0, 0, 0, 17) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |
| VX-561: Day 15 (n=0, 0, 0, 0, 0, 19) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) | 99999 (± 99999) |

| End point values | Part 2: VX-659/TEZ/IVA TC | Part 3: VX-659/TEZ/VX-561 TC | | |
|---|---------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 19 | | |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| VX-659: Day 15 (n=10, 16, 19, 0, 17, 17) | 835 (± 474) | 1140 (± 646) | | |
| VX-659: Day 29 (n=11, 19, 22, 0, 18, 19) | 1070 (± 914) | 923 (± 582) | | |
| TEZ: Day 15 (n=10, 16, 19, 7, 17, 17) | 1350 (± 1440) | 1000 (± 305) | | |
| TEZ: Day 29 (n=11, 19, 22, 11, 18, 19) | 955 (± 422) | 776 (± 321) | | |
| M1-TEZ: Day 15 (n=10, 16, 19, 7, 17, 19) | 4010 (± 1210) | 4060 (± 660) | | |
| M1-TEZ: Day 29 (n=11, 19, 22, 11, 18, 19) | 3810 (± 1120) | 3660 (± 1190) | | |
| IVA: Day 15 (n=10, 16, 19, 7, 17, 0) | 313 (± 158) | 99999 (± 99999) | | |
| IVA: Day 29 (n=11, 19, 22, 11, 18, 0) | 296 (± 175) | 99999 (± 99999) | | |

| | | | | |
|---|----------------------|----------------------|--|--|
| M1-IVA: Day 15 (n=10, 16, 19, 7, 17, 0) | 844 (\pm 622) | 99999 (\pm 99999) | | |
| M1-IVA Day 29 (n=11, 19, 22, 11, 18, 0) | 866 (\pm 691) | 99999 (\pm 99999) | | |
| VX-561: Day 15 (n=0, 0, 0, 0, 0, 17) | 99999 (\pm 99999) | 380 (\pm 240) | | |
| VX-561: Day 15 (n=0, 0, 0, 0, 0, 19) | 99999 (\pm 99999) | 288 (\pm 165) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 Through Safety Follow-up (up to Day 61 for Part 1, Day 85 for Part 2 and Day 57 for Part 3)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Part 1: Placebo |
|-----------------------|-----------------|

Reporting group description:

Subjects received placebo matched to VX-659/TEZ/IVA in TC treatment period for 4 weeks and placebo matched to TEZ/IVA in washout period for 4 days.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - Low Dose |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects received VX-659 80 mg qd/TEZ 100 mg qd/IVA 150 mg every 12 q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days.

| | |
|-----------------------|---|
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
|-----------------------|---|

Reporting group description:

Subjects received VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days.

| | |
|-----------------------|---------------------------------------|
| Reporting group title | Part 1: VX-659/TEZ/IVA TC - High Dose |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 days.

| | |
|-----------------------|-----------------|
| Reporting group title | Part 2: TEZ/IVA |
|-----------------------|-----------------|

Reporting group description:

Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks.

| | |
|-----------------------|---------------------------|
| Reporting group title | Part 2: VX-659/TEZ/IVA TC |
|-----------------------|---------------------------|

Reporting group description:

Following run-in period with TEZ 100 mg qd/IVA 150 mg q12h for 4 weeks, subjects received VX-659 400 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in TC treatment period for 4 weeks and TEZ 100 mg qd/IVA 150 mg q12h in washout period for 4 weeks.

| | |
|-----------------------|-----------------|
| Reporting group title | Part 3: Placebo |
|-----------------------|-----------------|

Reporting group description:

Subjects received placebo matched to VX-659/TEZ/VX-561 in TC treatment period for 4 weeks.

| | |
|-----------------------|------------------------------|
| Reporting group title | Part 3: VX-659/TEZ/VX-561 TC |
|-----------------------|------------------------------|

Reporting group description:

Subjects received VX-659 400 mg qd/TEZ 100 mg qd/VX-561 200 mg qd in TC treatment period for 4 weeks.

| Serious adverse events | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
|--|-----------------|--------------------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | 1 / 11 (9.09%) | 4 / 20 (20.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 1 / 11 (9.09%) | 2 / 20 (10.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Part 1: VX-659/TEZ/IVA TC - High Dose | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC |
|--|---------------------------------------|-----------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 11 (18.18%) | 1 / 18 (5.56%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 11 (18.18%) | 1 / 18 (5.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC | |
|--|-----------------|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 19 (10.53%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| 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 | | | |
| Dyspnoea | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Part 1: Placebo | Part 1: VX-659/TEZ/IVA TC - Low Dose | Part 1: VX-659/TEZ/IVA TC - Medium Dose |
|---|-----------------|--------------------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 10 (80.00%) | 10 / 11 (90.91%) | 15 / 20 (75.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| Fibroadenoma of breast subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 1 / 11 (9.09%) 1 | 1 / 20 (5.00%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 2 / 11 (18.18%) 2 | 2 / 20 (10.00%) 2 |
| Pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Application site rash subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Exercise tolerance decreased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Reproductive system and breast disorders Testicular pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 3 / 11 (27.27%) | 6 / 20 (30.00%) |
| occurrences (all) | 1 | 3 | 6 |
| Sputum increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 11 (18.18%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 11 (18.18%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Respiration abnormal | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 1 / 11 (9.09%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Lower respiratory tract congestion | | | |

| | | | |
|--------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 11 (18.18%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rales | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sputum discoloured | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Throat tightness | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Psychiatric disorders Irritability subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 11 (9.09%) 1 | 1 / 20 (5.00%) 1 |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 1 / 11 (9.09%) 1 | 0 / 20 (0.00%) 0 |
| Bacterial test positive subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| International normalised ratio increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Prothrombin time prolonged subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Activated partial thromboplastin time | | | |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| prolonged | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood glucose decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood chloride decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood glucose fluctuation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood sodium decreased | | | |

| | | | |
|------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Coronavirus test positive | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Crystal urine present | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Glucose urine present | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Red blood cells urine positive | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary sediment present | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|--------------------------------------|-----------------|----------------|-----------------|
| complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 4 / 20 (20.00%) |
| occurrences (all) | 0 | 1 | 4 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinus headache | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear congestion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Motion sickness subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 20 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 11 (9.09%) 1 | 1 / 20 (5.00%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Faeces discoloured subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Food poisoning subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Pancreatic failure | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Parotid gland enlargement subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Salivary hypersecretion subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Acne subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Skin disorder subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Flank pain | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 2 / 11 (18.18%) 2 | 1 / 20 (5.00%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 2 / 11 (18.18%) 2 | 1 / 20 (5.00%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Chronic sinusitis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Genital infection fungal subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Lower respiratory tract infection | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 11 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Part 1: VX-659/TEZ/IVA TC - High Dose | Part 2: TEZ/IVA | Part 2: VX-659/TEZ/IVA TC |
|---|---------------------------------------|-----------------|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 22 (77.27%) | 8 / 11 (72.73%) | 15 / 18 (83.33%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| Fibroadenoma of breast subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 1 / 11 (9.09%) 1 | 2 / 18 (11.11%) 2 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 18 (0.00%) 0 |
| Pain subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 1 / 11 (9.09%) 1 | 0 / 18 (0.00%) 0 |
| Application site rash subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Exercise tolerance decreased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Influenza like illness subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Reproductive system and breast disorders Testicular pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 2 / 11 (18.18%) | 4 / 18 (22.22%) |
| occurrences (all) | 5 | 2 | 4 |
| Sputum increased | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 1 / 11 (9.09%) | 3 / 18 (16.67%) |
| occurrences (all) | 4 | 2 | 3 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 0 / 11 (0.00%) | 2 / 18 (11.11%) |
| occurrences (all) | 4 | 0 | 2 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 1 | 1 |
| Respiration abnormal | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 4 / 18 (22.22%) |
| occurrences (all) | 0 | 0 | 4 |
| Sinus congestion | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lower respiratory tract congestion | | | |

| | | | |
|--------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 2 / 18 (11.11%) |
| occurrences (all) | 0 | 1 | 2 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paranasal sinus discomfort | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Rales | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 2 |
| Sinus pain | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sputum discoloured | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Throat irritation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Throat tightness | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Psychiatric disorders Irritability subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 2 / 11 (18.18%) 3 | 1 / 18 (5.56%) 1 |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 4 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 1 / 18 (5.56%) 1 |
| Bacterial test positive subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 1 / 18 (5.56%) 2 |
| International normalised ratio increased subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 2 |
| Prothrombin time prolonged subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Activated partial thromboplastin time | | | |

| | | | |
|---------------------------------------|----------------|----------------|----------------|
| prolonged | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood chloride decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood glucose fluctuation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood sodium decreased | | | |

| | | | |
|------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Coronavirus test positive | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Crystal urine present | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 11 (9.09%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glucose urine present | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Red blood cells urine positive | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary sediment present | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|--------------------------------------|-----------------|----------------|-----------------|
| complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 0 / 11 (0.00%) | 3 / 18 (16.67%) |
| occurrences (all) | 4 | 0 | 3 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus headache | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear congestion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| Motion sickness subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 2 / 11 (18.18%) 2 | 2 / 18 (11.11%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 2 / 11 (18.18%) 2 | 2 / 18 (11.11%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 2 / 18 (11.11%) 2 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 1 / 18 (5.56%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 2 / 18 (11.11%) 2 |
| Flatulence subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Faeces discoloured subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Food poisoning subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 18 (0.00%) 0 |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Pancreatic failure | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 18 (0.00%) 0 |
| Parotid gland enlargement subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Salivary hypersecretion subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 2 / 18 (11.11%) 2 |
| Acne subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 18 (0.00%) 0 |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Skin disorder subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Renal and urinary disorders | | | |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 1 / 18 (5.56%) 1 |
| Flank pain | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Intervertebral disc protrusion subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 1 / 11 (9.09%) 1 | 4 / 18 (22.22%) 4 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 3 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 0 / 11 (0.00%) 0 | 2 / 18 (11.11%) 2 |
| Sinusitis subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 0 / 18 (0.00%) 0 |
| Chronic sinusitis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 18 (0.00%) 0 |
| Genital infection fungal subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 18 (5.56%) 1 |
| Lower respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 11 (0.00%) | 0 / 18 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------|------------------------------|--|
| Non-serious adverse events | Part 3: Placebo | Part 3: VX-659/TEZ/VX-561 TC | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 18 / 19 (94.74%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|--|--|--|
| Fibroadenoma of breast subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Vascular disorders Hot flush subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Application site rash subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Exercise tolerance decreased subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 | 3 / 19 (15.79%) 3 0 / 19 (0.00%) 0 2 / 19 (10.53%) 2 1 / 19 (5.26%) 1 0 / 19 (0.00%) 0 0 / 19 (0.00%) 0 | |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Reproductive system and breast disorders Testicular pain | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 4 / 19 (21.05%) | |
| occurrences (all) | 2 | 5 | |
| Sputum increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiration abnormal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinus congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lower respiratory tract congestion | | | |

| | | |
|--------------------------------|----------------|----------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 |
| Productive cough | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Wheezing | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Paranasal sinus discomfort | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Rales | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 |
| Rhinorrhoea | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Sinus pain | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Sputum discoloured | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Bronchospasm | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 |
| Epistaxis | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Nasal discharge discolouration | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Throat irritation | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 |
| Throat tightness | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Psychiatric disorders Irritability subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 2 | 0 / 19 (0.00%) 0 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 19 (0.00%) 0 | |
| Bacterial test positive subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Blood glucose increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| International normalised ratio increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 19 (0.00%) 0 | |
| Prothrombin time prolonged subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Activated partial thromboplastin time | | | |

| | | | |
|---------------------------------------|----------------|----------------|--|
| prolonged | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pulmonary function test decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood chloride decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatinine decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood glucose fluctuation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood sodium decreased | | | |

| | | | |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Coronavirus test positive | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Crystal urine present | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Glucose urine present | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Monocyte count increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Red blood cells urine positive | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Urinary sediment present | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural | | | |

| | | | |
|--------------------------------------|----------------|----------------|--|
| complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Wound | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 19 (5.26%) | |
| occurrences (all) | 1 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 2 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinus headache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 2 | |
| Ear congestion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|--------------------|----------------------|--|
| Motion sickness subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 19 (10.53%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 2 | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Flatulence subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Faeces discoloured subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Food poisoning subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Pancreatic failure | | | |

| | | | |
|---|--------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Parotid gland enlargement subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Salivary hypersecretion subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Toothache subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 2 / 19 (10.53%) 2 | |
| Acne subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Skin disorder subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Micturition urgency subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 0 / 19 (0.00%) 0 | |
| Flank pain | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Chronic sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Genital infection fungal | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lower respiratory tract infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Increased appetite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 30 June 2017 | Added study drug doses, revised elements of the study design including treatment arms, sample size, and study duration, and revised inclusion/exclusion criteria. |
| 01 September 2017 | Added Part 3 to evaluate VX-659 in triple combination with TEZ/VX-561. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported