# Clinical trial results:
# A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

## Summary

| | |
|---|---|
| EudraCT number | 2017-004132-11 |
| Trial protocol | GB DE DK IE ES PL |
| Global end of trial date | 05 February 2019 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 05 June 2020 |
| First version publication date | 20 November 2019 |
| Version creation reason | • New data added to full data set<br>Updating secondary endpoints |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | VX17-659-102 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03447249 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-002191-PIP02-17 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 25 February 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 February 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for the F508del and a minimal function mutation (F/MF subjects).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 07 March 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | United States: 203 |
| Country: Number of subjects enrolled | Australia: 35 |
| Country: Number of subjects enrolled | United Kingdom: 24 |
| Country: Number of subjects enrolled | Israel: 19 |
| Country: Number of subjects enrolled | Ireland: 16 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Germany: 51 |
| Worldwide total number of subjects | 385 |
| EEA total number of subjects | 112 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 94 |
| Adults (18-64 years) | 291 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

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

Dosage and administration details:

Subjects received placebo matched to VX-659/TEZ/IVA once daily in the morning.

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | VX-659/TEZ/IVA TC |

Arm description:

Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | VX-659/TEZ/IVA |
| Investigational medicinal product code | VX-659/VX-661/VX-770 |
| Other name | VX-659/Tezacaftor/Ivacaftor fixed dose combination |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received VX-659/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.

| **Number of subjects in period 1[1]** | Placebo | VX-659/TEZ/IVA TC |
|---|---|---|
| Started | 190 | 192 |
| Completed | 185 | 192 |
| Not completed | 5 | 0 |
| Other | 3 | - |
| Adverse event | 1 | - |
| Withdrawal of consent (not due to AE) | 1 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In the above disposition summary, data are presented for 382 subjects who were randomized and dosed in the TC treatment period. Three subjects were enrolled into the study and randomized but were not dosed in the TC treatment period. Therefore, the total number of enrolled subjects is 385 but the number of subjects reported in subject disposition and baseline is 382.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period. | |
| Reporting group title | VX-659/TEZ/IVA TC |
| Reporting group description: | |
| Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period. | |

| Reporting group values | Placebo | VX-659/TEZ/IVA TC | Total |
|---|---|---|---|
| Number of subjects | 190 | 192 | 382 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 27.1 | 26.7 | |
| standard deviation | ± 10.0 | ± 9.8 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 83 | 85 | 168 |
| Male | 107 | 107 | 214 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 7 | 6 | 13 |
| Not Hispanic or Latino | 181 | 184 | 365 |
| Unknown or Not Reported | 2 | 2 | 4 |
| Race<br>Units: Subjects | | | |
| White | 187 | 188 | 375 |
| Black or African American | 1 | 2 | 3 |
| Both White and Black/African American | 2 | 2 | 4 |
| 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. All randomized subjects who carried the intended CF transmembrane conductance regulator gene (CFTR) allele mutation and received at least 1 dose of study drug in the TC Treatment Period. | | | |
| Units: Percentage points | | | |
| arithmetic mean | 60.4 | 60.7 | |
| standard deviation | ± 14.5 | ± 15.4 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period. | |
| Reporting group title | VX-659/TEZ/IVA TC |
| Reporting group description: | |
| Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period. | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Subjects who received placebo matched to VX-659/TEZ/IVA in the morning and placebo matched to IVA in the evening for 24 weeks in the TC treatment period. | |
| Subject analysis set title | VX-659/TEZ/IVA TC |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Subjects who received VX-659 240 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA 150 mg as mono tablet in the evening for 24 weeks in the TC treatment period. | |

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

| | |
|---|---|
| End point title | Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) |
| End point description: | |
| 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 who carried the intended CFTR allele mutation and received at least 1 dose of study drug in the TC Treatment Period. | |
| End point type | Primary |
| End point timeframe: | |
| From Baseline through Week 24 | |

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: percentage points | | | | |
| least squares mean (standard error) | -0.8 (± 0.6) | 13.4 (± 0.6) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis |
| Comparison groups | VX-659/TEZ/IVA TC v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 14.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.6 |
| upper limit | 15.7 |

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

| | |
|---|---|
| End point title | Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) |

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Analysis population included all subjects in the Full Analysis Set (all randomized subjects who carried the intended CFTR allele mutation and received at least 1 dose of study drug) who completed the Week 4 Visit or were randomized at least 28 days before the data cutoff date.

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

End point timeframe:

From Baseline at Week 4

| **End point values** | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: percentage points | | | | |
| least squares mean (standard error) | -1.0 (± 0.6) | 13.0 (± 0.6) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis |
|---|---|

Statistical analysis description:

The data presented for this endpoint was based on interim analysis at Week 4.

| | |
|---|---|
| Comparison groups | VX-659/TEZ/IVA TC v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.4 |
| upper limit | 15.7 |

## Secondary: Number of Pulmonary Exacerbations (PEx)

| | |
|---|---|
| End point title | Number of Pulmonary Exacerbations (PEx) |

End point description:

Pulmonary exacerbation was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. FAS.

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

End point timeframe:

From Baseline through Week 24

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: pulmonary exacerbation events | 116 | 17 | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Negative binomial regression model |
| Parameter estimate | Rate ratio |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.09 |
| upper limit | 0.24 |

## Secondary: Absolute Change in Sweat Chloride (SwCl)

| End point title | Absolute Change in Sweat Chloride (SwCl) |
|---|---|
| End point description: | |
| Sweat samples were collected using an approved collection device. FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline through Week 24 | |

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: millimole per liter (mmol/L) | | | | |
| least squares mean (standard error) | -0.1 (± 1.0) | -44.6 (± 0.9) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | -44.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -47.2 |
| upper limit | -41.9 |

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

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

| **End point values** | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -1.5 (± 1.1) | 18.6 (± 1.0) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 20.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 17.2 |
| upper limit | 23 |

**Secondary: Absolute Change in Body Mass Index (BMI)**

| End point title | Absolute Change in Body Mass Index (BMI) |
|---|---|
| End point description: | |
| BMI was defined as weight in kilogram (kg) divided by height in square meter (m^2). FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline at Week 24 | |

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: kilogram per meter square (kg/m^2) | | | | |
| least squares mean (standard error) | -0.05 (± 0.07) | 1.06 (± 0.07) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.31 |

**Secondary: Absolute Change in Sweat Chloride**

| | |
|---|---|
| End point title | Absolute Change in Sweat Chloride |
| End point description: | |
| Sweat samples were collected using an approved collection device. FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| From Baseline at Week 4 | |

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 0.0 (± 1.0) | -43.3 (± 1.0) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | -43.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -46.3 |
| upper limit | -40.5 |

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

| End point title | Absolute Change in Cystic Fibrosis Questionnaire Revised (CFQ-R) Respiratory Domain Score |
|---|---|

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 Week 4

| **End point values** | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 0.1 (± 1.2) | 18.0 (± 1.2) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |

| | |
|---|---|
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Mixed-effects model for repeated measure |
| Parameter estimate | LS Mean Difference |
| Point estimate | 17.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.5 |
| upper limit | 21.3 |

## Secondary: Time-to-first Pulmonary Exacerbation (PEx)

| | |
|---|---|
| End point title | Time-to-first Pulmonary Exacerbation (PEx) |

End point description:

Pulmonary exacerbation was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. FAS. Here 99999 represents that Median and 95% confidence interval could not be estimated because less than 50% of subjects had events.

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

End point timeframe:

From Baseline through Week 24

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Change in BMI Z-score for Subjects <=20 Years of Age at Baseline

| | |
|---|---|
| End point title | Absolute Change in BMI Z-score for Subjects <=20 Years of Age at Baseline |

End point description:

BMI was defined as weight in kg divided by height in m^2. z-score is a statistical measure to describe whether a mean was above or below the standard. BMI, adjusted for age and sex, was analyzed as BMI-for-age z-score. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Higher values are indicative of higher BMI. FAS. Here "Overall Number of Subjects Analyzed" signifies those subjects

who were <=20 years of age at Baseline.

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

End point timeframe:
From Baseline at Week 24

| **End point values** | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 58 | | |
| Units: kg/m^2 | | | | |
| least squares mean (standard error) | -0.08 (± 0.05) | 0.31 (± 0.05) | | |

**Statistical analyses**

| **Statistical analysis title** | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 117 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | LS Mean Difference |
| Point estimate | 0.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.24 |
| upper limit | 0.54 |

**Secondary: Absolute Change in Body Weight**

| End point title | Absolute Change in Body Weight |
|---|---|

End point description:
FAS.

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

End point timeframe:
From Baseline at Week 24

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 190 | 192 | | |
| Units: kg | | | | |
| least squares mean (standard error) | 0.1 (± 0.2) | 3.3 (± 0.2) | | |

**Statistical analyses**

| Statistical analysis title | Statistical Analysis |
|---|---|
| Comparison groups | Placebo v VX-659/TEZ/IVA TC |
| Number of subjects included in analysis | 382 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | LS Mean Difference |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.7 |
| upper limit | 3.8 |

**Secondary: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)**

| End point title | Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|---|---|

End point description:

Adverse events are presented as per Safety Set. Group assignments for subjects in the Safety Set were based on actual treatment received, such that 1 subject assigned to Placebo group who inadvertently received one or more doses of VX-659/TEZ/IVA TC regimen was included in VX-659/TEZ/IVA TC group for the purpose of safety analysis.

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

End point timeframe:

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

| End point values | Placebo | VX-659/TEZ/IVA TC | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 189 | 193 | | |
| Units: subjects | | | | |
| Subjects with TEAEs | 175 | 173 | | |
| Subjects with Serious TEAEs | 58 | 11 | | |

## Statistical analyses

No statistical analyses for this end point

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

| End point title | Observed Pre-dose Concentration (Ctrough) of VX-659, TEZ, M1-TEZ, and IVA[1] |
|---|---|

End point description:

Pharmacokinetic (PK) set included all randomized subjects who carried the intended CFTR allele mutation and received at least 1 dose of study drug in the TC Treatment Period. Here "n" signifies those subjects who were evaluable for this outcome measure at specified time points.

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

End point timeframe:

Pre-dose on Week 4, 8, 12, and 16

Notes:

[1] - 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: Observed Pre-dose Concentration was calculated only for triple combination (TC) arm.

| **End point values** | VX-659/TEZ/IVA TC | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 192 | | | |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| VX-659: Week 4 (n = 150) | 662 (± 528) | | | |
| VX-659: Week 8 (n = 148) | 764 (± 1520) | | | |
| VX-659: Week 12 (n = 144) | 614 (± 519) | | | |
| VX-659: Week 16 (n = 162) | 638 (± 521) | | | |
| TEZ: Week 4 (n = 150) | 1220 (± 645) | | | |
| TEZ: Week 8 (n = 148) | 1390 (± 1250) | | | |
| TEZ: Week 12 (n = 142) | 1290 (± 766) | | | |
| TEZ: Week 16 (n = 161) | 1220 (± 654) | | | |
| M1-TEZ: Week 4 (n = 150) | 4380 (± 1560) | | | |
| M1-TEZ: Week 8 (n = 148) | 4580 (± 1480) | | | |
| M1-TEZ: Week 12 (n = 142) | 4580 (± 1530) | | | |
| M1-TEZ: Week 16 (n = 161) | 4420 (± 1520) | | | |
| IVA: Week 4 (n = 150) | 442 (± 277) | | | |
| IVA: Week 8 (n = 148) | 548 (± 1100) | | | |
| IVA: Week 12 (n = 142) | 429 (± 327) | | | |
| IVA: Week 16 (n = 161) | 416 (± 303) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Adverse events are presented as per Safety Set. Treatment assignments for subjects in the Safety Set are based on actual treatment received, such that all subjects who received at least 1 dose of VX-659/TEZ/IVA TC were included in the VX-659/TEZ/IVA TC group for the safety analysis, even if they were assigned to the placebo group.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

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

Reporting group description:

Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

| | |
|---|---|
| Reporting group title | VX-659/TEZ/IVA TC |

Reporting group description:

Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

| Serious adverse events | Placebo | VX-659/TEZ/IVA TC | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 58 / 189 (30.69%) | 11 / 193 (5.70%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 189 (1.59%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax spontaneous | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Intentional self-injury | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device damage | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax traumatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Cystic fibrosis related diabetes | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right-to-left cardiac shunt | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Distal intestinal obstruction syndrome | | | |
| subjects affected / exposed | 2 / 189 (1.06%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Axillary mass | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 45 / 189 (23.81%) | 3 / 193 (1.55%) | |
| occurrences causally related to treatment / all | 1 / 55 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 2 / 189 (1.06%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysentery | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective exacerbation of bronchiectasis | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 189 (0.00%) | 1 / 193 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular device infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 189 (0.53%) | 0 / 193 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | VX-659/TEZ/IVA TC | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 166 / 189 (87.83%) | 141 / 193 (73.06%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 189 (1.06%) | 17 / 193 (8.81%) | |
| occurrences (all) | 3 | 20 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 7 / 189 (3.70%) | 13 / 193 (6.74%) | |
| occurrences (all) | 7 | 15 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 189 (2.12%) | 16 / 193 (8.29%) | |
| occurrences (all) | 5 | 19 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 31 / 189 (16.40%) | 26 / 193 (13.47%) | |
| occurrences (all) | 37 | 30 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 189 (7.94%) | 13 / 193 (6.74%) | |
| occurrences (all) | 16 | 13 | |
| Fatigue | | | |
| subjects affected / exposed | 19 / 189 (10.05%) | 9 / 193 (4.66%) | |
| occurrences (all) | 19 | 12 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 189 (8.47%) | 17 / 193 (8.81%) | |
| occurrences (all) | 21 | 20 | |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 24 / 189 (12.70%) | 8 / 193 (4.15%) | |
| occurrences (all) | 31 | 11 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 10 / 189 (5.29%) | 3 / 193 (1.55%) | |
| occurrences (all) | 14 | 3 | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 189 (5.82%) | 7 / 193 (3.63%) | |
| occurrences (all) | 11 | 7 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 189 (2.65%) | 11 / 193 (5.70%) | |
| occurrences (all) | 5 | 11 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 68 / 189 (35.98%) | 34 / 193 (17.62%) | |
| occurrences (all) | 100 | 42 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 13 / 189 (6.88%) | 20 / 193 (10.36%) | |
| occurrences (all) | 14 | 24 | |
| Sputum increased | | | |
| subjects affected / exposed | 38 / 189 (20.11%) | 28 / 193 (14.51%) | |
| occurrences (all) | 43 | 32 | |
| Haemoptysis | | | |
| subjects affected / exposed | 19 / 189 (10.05%) | 6 / 193 (3.11%) | |
| occurrences (all) | 21 | 6 | |
| Nasal congestion | | | |
| subjects affected / exposed | 11 / 189 (5.82%) | 11 / 193 (5.70%) | |
| occurrences (all) | 11 | 11 | |
| Respiration abnormal | | | |
| subjects affected / exposed | 14 / 189 (7.41%) | 7 / 193 (3.63%) | |
| occurrences (all) | 16 | 9 | |
| Productive cough | | | |
| subjects affected / exposed | 14 / 189 (7.41%) | 3 / 193 (1.55%) | |
| occurrences (all) | 22 | 4 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Rash | | | |
| subjects affected / exposed | 10 / 189 (5.29%) | 10 / 193 (5.18%) | |
| occurrences (all) | 16 | 12 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 79 / 189 (41.80%) | 21 / 193 (10.88%) | |
| occurrences (all) | 103 | 23 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 189 (3.70%) | 35 / 193 (18.13%) | |
| occurrences (all) | 7 | 41 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 16 / 189 (8.47%) | 26 / 193 (13.47%) | |
| occurrences (all) | 19 | 33 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 January 2018 | Updated study drug regimen, dosing guidance, dose and population rationale |
| 27 April 2018 | Revised exclusion criteria |
| 01 October 2018 | A European-specific version of the protocol was created with a 24-week primary endpoint |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported