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 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 Units: Subjects			
Age continuous Units: years			
arithmetic mean	27.1	26.7	
standard deviation	± 10.0	± 9.8	-
Gender categorical Units: Subjects			
Female	83	85	168
Male	107	107	214
Ethnicity Units: Subjects			
Hispanic or Latino	7	6	13
Not Hispanic or Latino	181	184	365
Unknown or Not Reported	2	2	4
Race 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