



Clinical trial results:

A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2017-002968-40
Trial protocol	GB IE BE DE FR DK PL
Global end of trial date	29 September 2023

Results information

Result version number	v1 (current)
This version publication date	13 April 2024
First version publication date	13 April 2024

Trial information

Trial identification

Sponsor protocol code	VX17-661-116
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03537651
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001640-PIP01-14
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 October 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of TEZ/IVA in subjects with CF aged 6 years and older, who are homozygous or heterozygous for F508del in Part A

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	67 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	130
EEA total number of subjects	38

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	130
Adolescents (12-17 years)	0
Adults (18-64 years)	0
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 cystic fibrosis (CF) subjects aged 6 years or older who participated in parent Studies VX15-661-113 Part B (Study 113B; NCT02953314) or VX16-661-115 (Study 115; NCT03559062). Eligible subjects from parent studies were enrolled in Study 116.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A: TEZ/IVA
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Arm description:

Subjects weighing less than (<)40 kilograms (kg) at Day 1 received tezacaftor (TEZ) 50 milligrams (mg) once daily (qd)/ivacaftor (IVA) 75 mg every 12 hours (q12h) and the subjects weighing greater than or equals to (>=) 40 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks. Doses were adjusted upward for changes in body weight and/or age.

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

Dosage and administration details:

Subjects received TEZ/IVA fixed-dose combination 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	Part A: TEZ/IVA
Started	130
113B/116 FAS	64 ^[1]
113B/116 LCI FAS	30 ^[2]
115/116 FAS	66 ^[3]
115/116 FAS (TEZ/IVA Group)	53 ^[4]
Completed	69
Not completed	61

Adverse Event	2
Other	1
Commercial Drug is Available for Participant	56
Withdrawal of Consent (not due to AE)	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All enrolled subjects from parent Study 113B who received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All enrolled subjects who participated in the LCI sub study in parent Study 113B and received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All enrolled subjects who were randomized to either TEZ/IVA, IVA or placebo treatment group in parent Study 115 and received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: All enrolled subjects who were randomized to the TEZ/IVA treatment group in parent Study 115 and received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype.

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part B: TEZ/IVA
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Arm description:

Subjects weighing <30 kg at Day 1 received TEZ 50 mg qd/IVA 75 mg q12h and the subjects weighing >=30 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 192 weeks. Doses were adjusted upward for changes in body weight and/or age.

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

Dosage and administration details:

Subjects received TEZ/IVA fixed-dose combination 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 2^[5]	Part B: TEZ/IVA
Started	62
113B/116 FAS	9
115/116 FAS	53
Completed	3
Not completed	59
Adverse Event	1
Other	1
Commercial Drug is available for Subject	56
Withdrawal of Consent (not due to AE)	1

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 130 subjects were enrolled in the parent study on Part A. However, only 62 subjects rolled over to Part B from Part A of the study.

Baseline characteristics

Reporting groups

Reporting group title	Part A: TEZ/IVA
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Reporting group description:

Subjects weighing less than (<)40 kilograms (kg) at Day 1 received tezacaftor (TEZ) 50 milligrams (mg) once daily (qd)/ivacaftor (IVA) 75 mg every 12 hours (q12h) and the subjects weighing greater than or equals to (>=) 40 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks. Doses were adjusted upward for changes in body weight and/or age.

Reporting group values	Part A: TEZ/IVA	Total	
Number of subjects	130	130	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	8.3 ± 1.7	-	
Gender categorical Units: Subjects			
Female	67	67	
Male	63	63	
Ethnicity Units: Subjects			
Hispanic or Latino	4	4	
Not Hispanic or Latino	119	119	
Not Collected per Local Regulations	7	7	
Race Units: Subjects			
White	125	125	
Black or African American	1	1	
Asian	1	1	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Not Collected per Local Regulations	2	2	
Other	1	1	

End points

End points reporting groups

Reporting group title	Part A: TEZ/IVA
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Reporting group description:

Subjects weighing less than (<)40 kilograms (kg) at Day 1 received tezacaftor (TEZ) 50 milligrams (mg) once daily (qd)/ivacaftor (IVA) 75 mg every 12 hours (q12h) and the subjects weighing greater than or equals to (>=) 40 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks. Doses were adjusted upward for changes in body weight and/or age.

Reporting group title	Part B: TEZ/IVA
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Reporting group description:

Subjects weighing <30 kg at Day 1 received TEZ 50 mg qd/IVA 75 mg q12h and the subjects weighing >=30 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 192 weeks. Doses were adjusted upward for changes in body weight and/or age.

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

End point title	Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
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End point description:

Safety Set included all subjects who were enrolled and received at least 1 dose of TEZ/IVA in Part A of Study 116.

End point type	Primary
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End point timeframe:

Day 1 up to Week 100

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 the safety endpoint.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	130			
Units: Subjects				
Subjects with TEAEs	129			
Subjects with SAEs	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Lung Clearance Index 2.5 (LCI2.5) for 115/116 FAS (TEZ/IVA Group)

End point title	Part A: Absolute Change in Lung Clearance Index 2.5 (LCI2.5) for 115/116 FAS (TEZ/IVA Group)
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End point description:

The LCI2.5 index is the number of lung turnovers required to reduce the end tidal inert gas

concentration to 1/40th of its starting values and is calculated by dividing the sum of exhaled tidal breaths (cumulative exhaled volume (CEV)) by simultaneously measured functional residual capacity (FRC). An LCI of 7.5 and below is normal; values greater than 7.5 are abnormal. LCI is able to detect abnormalities in lung function earlier than more traditional modalities such as spirometry. 115/116 Full analysis set (FAS) (TEZ/IVA group) included all enrolled participants who were randomized to the TEZ/IVA treatment group in parent Study 115 and received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype. As pre-specified in the SAP, model-based efficacy analysis for participants from parent Study 115 was planned only for the TEZ/IVA treatment group.

End point type	Secondary
End point timeframe:	
From Parent Study 115 Baseline at Week 96 (Study 116)	

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: Index				
least squares mean (confidence interval 95%)	-0.95 (-1.38 to -0.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in LCI2.5 for 113B/116 LCI FAS

End point title	Part A: Absolute Change in LCI2.5 for 113B/116 LCI FAS
End point description:	
<p>The LCI2.5 index is the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting values and is calculated by dividing the sum of exhaled tidal breaths (cumulative exhaled volume (CEV)) by simultaneously measured functional residual capacity (FRC). An LCI of 7.5 and below is normal; values greater than 7.5 are abnormal. LCI is able to detect abnormalities in lung function earlier than more traditional modalities such as spirometry. 13B/116 LCI FAS included all enrolled participants who participated in the LCI sub study in parent Study 113B and received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype. As pre-specified in the SAP, only descriptive summary statistics were planned to be reported for the 113B/116 LCI FAS.</p>	
End point type	Secondary
End point timeframe:	
From Parent Study 113B Baseline at Week 96 (Study 116)	

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Index				
arithmetic mean (standard deviation)	-2.04 (± 1.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Sweat Chloride (SwCl) for 115/116 FAS (TEZ/IVA Group)

End point title	Part A: Absolute Change in Sweat Chloride (SwCl) for 115/116 FAS (TEZ/IVA Group)
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End point description:

Sweat samples were collected using an approved collection device.115/116 FAS (TEZ/IVA group). As pre-specified in the SAP, model-based efficacy analysis for participants from parent Study 115 was planned only for the TEZ/IVA treatment group.

End point type	Secondary
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End point timeframe:

From Parent Study 115 Baseline at Week 96 (Study 116)

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-13.8 (-17.7 to -9.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in SwCl for 113B/116 FAS

End point title	Part A: Absolute Change in SwCl for 113B/116 FAS
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End point description:

Sweat samples were collected using an approved collection device.113B/116 FAS included all enrolled subjects from parent Study 113B who received at least 1 dose of TEZ/IVA in Study 116 and had an eligible genotype.

End point type	Secondary
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End point timeframe:

From Parent Study 113B Baseline at Week 96 (Study 116)

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: mmol/L				
least squares mean (confidence interval 95%)	-16.2 (-21.9 to -10.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 115/116 FAS (TEZ/IVA Group)

End point title	Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 115/116 FAS (TEZ/IVA Group)
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End point description:

The CFQ-R is a validated participant-reported outcome measuring health-related quality of life for participants with CF. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life.115/116 FAS (TEZ/IVA group). As pre-specified in the SAP, model-based efficacy analysis for participants from parent Study 115 was planned only for the TEZ/IVA treatment group.

End point type	Secondary
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End point timeframe:

From Parent Study 115 Baseline at Week 96 (Study 116)

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: units on a scale				
least squares mean (confidence interval 95%)	6.4 (3.5 to 9.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in CFQ-R Respiratory Domain Score for 113B/116 FAS

End point title	Part A: Absolute Change in CFQ-R Respiratory Domain Score for 113B/116 FAS
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End point description:

The CFQ-R is a validated participant-reported outcome measuring health-related quality of life for participants with CF. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life.113B/116 FAS.

End point type	Secondary
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End point timeframe:

From Parent Study 113B Baseline at Week 96 (Study 116)

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: units on a scale				
least squares mean (confidence interval 95%)	6.0 (1.1 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Mass Index (BMI) for 115/116 FAS (TEZ/IVA Group)

End point title	Part A: Absolute Change in Body Mass Index (BMI) for 115/116 FAS (TEZ/IVA Group)
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End point description:

BMI was defined as weight in kilograms (kg) divided by squared height in meters (m²).115/116 FAS (TEZ/IVA group). As pre-specified in the SAP, model-based efficacy analysis for participants from parent Study 115 was planned only for the TEZ/IVA treatment group.

End point type	Secondary
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End point timeframe:

From Parent Study 115 Baseline at Week 96 (Study 116)

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: kilogram per meter square (kg/m ²)				
least squares mean (confidence interval 95%)	1.25 (1.00 to 1.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in BMI for 113B/116 FAS

End point title	Part A: Absolute Change in BMI for 113B/116 FAS
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End point description:

BMI was defined as weight in kg divided by m².113B/116 FAS.

End point type	Secondary
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End point timeframe:

From Parent Study 113B Baseline at Week 96 (Study 116)

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: kg/m ²				
least squares mean (confidence interval 95%)	1.19 (0.74 to 1.64)			

Statistical analyses

No statistical analyses for this end point

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

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

Safety Set included all subjects who were enrolled and received at least 1 dose of TEZ/IVA in Part B of Study 116.

End point type	Secondary
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End point timeframe:

Day 1 up to Week 192

End point values	Part B: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: Subjects				
Subjects With TEAEs	53			
Subjects With SAEs	8			

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 Visit (up to Week 100 for Part A, and up to Week 192 for Part B)

Adverse event reporting additional description:

Safety Set included all subjects who were enrolled and received at least 1 dose of TEZ/IVA in Study 116. MedDRA version 23.1 applied for Part A, MedDRA version 26.1 applied for Part B.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1,26.1
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Reporting groups

Reporting group title	Part A: TEZ/IVA
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Reporting group description:

Subjects weighing <40 kg at Day 1 received TEZ 50 mg qd/IVA 75 mg q12h and the subjects weighing >= 40 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks. Doses were adjusted upward for changes in body weight and/or age.

Reporting group title	Part B: TEZ/IVA
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Reporting group description:

Subjects weighing <30 kg at Day 1 received TEZ 50 mg qd/IVA 75 mg q12h and the subjects weighing >=30 kg at Day 1 received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 192 weeks. Doses were adjusted upward for changes in body weight and/or age.

Serious adverse events	Part A: TEZ/IVA	Part B: TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 130 (23.85%)	8 / 62 (12.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial test positive			

subjects affected / exposed	3 / 130 (2.31%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas test positive			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas test positive			
subjects affected / exposed	0 / 130 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 130 (1.54%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (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 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 130 (0.77%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus disorder			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoidal hypertrophy			

subjects affected / exposed	0 / 130 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus polyp			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (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			
Chronic sinusitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial disease carrier			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device related sepsis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	15 / 130 (11.54%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 21	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 130 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 130 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Weight gain poor			
subjects affected / exposed	1 / 130 (0.77%)	0 / 62 (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	Part A: TEZ/IVA	Part B: TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 130 (98.46%)	49 / 62 (79.03%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 130 (9.23%)	2 / 62 (3.23%)	
occurrences (all)	15	3	
Forced expiratory volume decreased			
subjects affected / exposed	7 / 130 (5.38%)	7 / 62 (11.29%)	
occurrences (all)	8	7	
Pseudomonas test positive			
subjects affected / exposed	11 / 130 (8.46%)	2 / 62 (3.23%)	
occurrences (all)	12	5	
Staphylococcus test positive			
subjects affected / exposed	3 / 130 (2.31%)	4 / 62 (6.45%)	
occurrences (all)	3	4	
Bacterial test positive			
subjects affected / exposed	19 / 130 (14.62%)	8 / 62 (12.90%)	
occurrences (all)	23	13	
Aspartate aminotransferase			

increased subjects affected / exposed occurrences (all)	8 / 130 (6.15%) 9	2 / 62 (3.23%) 2	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	20 / 130 (15.38%) 35	8 / 62 (12.90%) 12	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 7 26 / 130 (20.00%) 42	0 / 62 (0.00%) 0 3 / 62 (4.84%) 3	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	8 / 130 (6.15%) 8	0 / 62 (0.00%) 0	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting	10 / 130 (7.69%) 11 8 / 130 (6.15%) 11 20 / 130 (15.38%) 27 8 / 130 (6.15%) 8 8 / 130 (6.15%) 9	4 / 62 (6.45%) 6 1 / 62 (1.61%) 1 6 / 62 (9.68%) 10 0 / 62 (0.00%) 0 3 / 62 (4.84%) 5	

subjects affected / exposed occurrences (all)	21 / 130 (16.15%) 24	5 / 62 (8.06%) 6	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed occurrences (all)	14 / 130 (10.77%) 20	3 / 62 (4.84%) 3	
Cough			
subjects affected / exposed occurrences (all)	73 / 130 (56.15%) 157	15 / 62 (24.19%) 25	
Epistaxis			
subjects affected / exposed occurrences (all)	4 / 130 (3.08%) 5	4 / 62 (6.45%) 5	
Nasal congestion			
subjects affected / exposed occurrences (all)	24 / 130 (18.46%) 43	2 / 62 (3.23%) 2	
Nasal polyps			
subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 7	3 / 62 (4.84%) 3	
Oropharyngeal pain			
subjects affected / exposed occurrences (all)	24 / 130 (18.46%) 35	6 / 62 (9.68%) 8	
Productive cough			
subjects affected / exposed occurrences (all)	22 / 130 (16.92%) 29	6 / 62 (9.68%) 9	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed occurrences (all)	7 / 130 (5.38%) 9	0 / 62 (0.00%) 0	
Infections and infestations			
Otitis media			
subjects affected / exposed occurrences (all)	8 / 130 (6.15%) 13	4 / 62 (6.45%) 4	
Nasopharyngitis			
subjects affected / exposed occurrences (all)	24 / 130 (18.46%) 62	10 / 62 (16.13%) 15	
Influenza			

subjects affected / exposed	13 / 130 (10.00%)	0 / 62 (0.00%)
occurrences (all)	13	0
Infective pulmonary exacerbation of cystic fibrosis		
subjects affected / exposed	57 / 130 (43.85%)	10 / 62 (16.13%)
occurrences (all)	97	13
Gastroenteritis		
subjects affected / exposed	9 / 130 (6.92%)	2 / 62 (3.23%)
occurrences (all)	15	2
Ear infection		
subjects affected / exposed	8 / 130 (6.15%)	2 / 62 (3.23%)
occurrences (all)	9	2
COVID-19		
subjects affected / exposed	0 / 130 (0.00%)	15 / 62 (24.19%)
occurrences (all)	0	17
Bacterial disease carrier		
subjects affected / exposed	7 / 130 (5.38%)	6 / 62 (9.68%)
occurrences (all)	10	8
Rhinitis		
subjects affected / exposed	11 / 130 (8.46%)	4 / 62 (6.45%)
occurrences (all)	18	5
Pharyngitis streptococcal		
subjects affected / exposed	8 / 130 (6.15%)	0 / 62 (0.00%)
occurrences (all)	8	0
Pharyngitis		
subjects affected / exposed	8 / 130 (6.15%)	0 / 62 (0.00%)
occurrences (all)	8	0
Viral upper respiratory tract infection		
subjects affected / exposed	10 / 130 (7.69%)	3 / 62 (4.84%)
occurrences (all)	19	6
Upper respiratory tract infection		
subjects affected / exposed	31 / 130 (23.85%)	10 / 62 (16.13%)
occurrences (all)	54	13
Tonsillitis		
subjects affected / exposed	2 / 130 (1.54%)	4 / 62 (6.45%)
occurrences (all)	2	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2019	Amended to add an additional 96 weeks of treatment (Part B). The dose cutoff for weight-based dosing was revised.
13 October 2021	Amended to add an additional 96 weeks of TEZ/IVA treatment to Part B to further evaluate the long-term safety and tolerability of TEZ/IVA in subjects enrolled in Study VX17-661-116 Part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported