



Clinical trial results: A Phase 1/2 Study of VX-445 in Subjects With Cystic Fibrosis Summary

EudraCT number	2017-000797-11
Trial protocol	NL BE
Global end of trial date	27 March 2018

Results information

Result version number	v1
This version publication date	12 April 2019
First version publication date	12 April 2019

Trial information

Trial identification

Sponsor protocol code	VX16-445-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03227471
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 877 634 8789, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 877 634 8789, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2018
Global end of trial reached?	Yes
Global end of trial date	27 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability, and efficacy of VX-445 in triple combination (TC) with Tezacaftor/Ivacaftor (TEZ/IVA) or with TEZ/VX-561.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 88
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Belgium: 6
Worldwide total number of subjects	125
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	125
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included 6 parts: Part D, E, and F were conducted in adult subjects with cystic fibrosis (CF).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Part D: Placebo
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Arm description:

Subjects received placebo matched to VX-445/TEZ/IVA triple combination (TC) for 4 weeks in the TC treatment period.

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

Dosage and administration details:

Subjects received placebo matched to VX-445 once daily.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	Part D: VX-445/TEZ/IVA TC - Low Dose
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Arm description:

Subjects received VX-445/TEZ/IVA TC low dose for 4 weeks in the TC treatment period.

Arm type	Experimental
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Investigational medicinal product name	VX-445
Investigational medicinal product code	VX-445
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received VX-445 low dose once daily.	
Investigational medicinal product name	TEZ/IVA
Investigational medicinal product code	VX-661/VX-770
Other name	Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received TEZ/IVA once daily in the morning.	
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA once daily in the evening.	
Arm title	Part D: VX-445/TEZ/IVA TC - Medium Dose
Arm description:	
Subjects received VX-445/TEZ/IVA TC medium dose for 4 weeks in the TC treatment period.	
Arm type	Experimental
Investigational medicinal product name	VX-445
Investigational medicinal product code	VX-445
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received VX-445 medium dose once daily.	
Investigational medicinal product name	TEZ/IVA
Investigational medicinal product code	VX-661/VX-770
Other name	Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received TEZ/IVA once daily in the morning.	
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA once daily in the evening.	
Arm title	Part D: VX-445/TEZ/IVA TC - High Dose
Arm description:	
Subjects received VX-445/TEZ/IVA TC high dose for 4 weeks in the TC treatment period.	
Arm type	Experimental

Investigational medicinal product name	VX-445
Investigational medicinal product code	VX-445
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received VX-445 high dose once daily.	
Investigational medicinal product name	TEZ/IVA
Investigational medicinal product code	VX-661/VX-770
Other name	Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received TEZ/IVA once daily in the morning.	
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA once daily in the evening.	
Arm title	Part E: TEZ/IVA
Arm description:	
Following run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA and placebo matched to VX-445 for 4 weeks in the TC treatment period.	
Arm type	Active comparator
Investigational medicinal product name	Placebo (matched to VX-445)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received placebo matched to VX-445 once daily.	
Investigational medicinal product name	TEZ/IVA
Investigational medicinal product code	VX-661/VX-770
Other name	Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received TEZ/IVA once daily in the morning.	
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA once daily in the evening.	
Arm title	Part E: VX-445/TEZ/IVA TC
Arm description:	
Following run-in period of 4 weeks with TEZ/IVA, subjects received VX-445/TEZ/IVA for 4 weeks in the TC treatment period.	
Arm type	Experimental

Investigational medicinal product name	VX-445
Investigational medicinal product code	VX-445
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received VX-445 once daily.	
Investigational medicinal product name	TEZ/IVA
Investigational medicinal product code	VX-661/VX-770
Other name	Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received TEZ/IVA once daily in the morning.	
Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received IVA once daily in the evening.	
Arm title	Part F: Placebo
Arm description:	
Subjects received placebo matched to VX-445/TEZ/VX-561 for 4 weeks in the TC treatment period.	
Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-445)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received placebo matched to VX-445 once daily.	
Investigational medicinal product name	Placebo (matched to TEZ)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received placebo matched to TEZ once daily.	
Investigational medicinal product name	Placebo (matched to VX-561)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received placebo matched to VX-561 once daily.	
Arm title	Part F: VX-445/TEZ/VX-561 TC
Arm description:	
Subjects received VX-445/TEZ/VX-561 TC for 4 weeks in the TC treatment period.	
Arm type	Experimental

Investigational medicinal product name	VX-445
Investigational medicinal product code	VX-445
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received VX-445 once daily.	
Investigational medicinal product name	TEZ
Investigational medicinal product code	VX-661
Other name	Tezacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received TEZ once daily.	
Investigational medicinal product name	VX-561
Investigational medicinal product code	VX-561
Other name	CTP-656
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received VX-561 once daily.	

Number of subjects in period 1 ^[1]	Part D: Placebo	Part D: VX-445/TEZ/IVA TC - Low Dose	Part D: VX-445/TEZ/IVA TC - Medium Dose
Started	12	10	22
Completed	12	10	22
Not completed	0	0	0
Withdrawal of consent (not due to AE)	-	-	-

Number of subjects in period 1 ^[1]	Part D: VX-445/TEZ/IVA TC - High Dose	Part E: TEZ/IVA	Part E: VX-445/TEZ/IVA TC
Started	21	7	21
Completed	21	7	20
Not completed	0	0	1
Withdrawal of consent (not due to AE)	-	-	1

Number of subjects in period 1 ^[1]	Part F: Placebo	Part F: VX-445/TEZ/VX-561 TC
Started	8	21
Completed	8	21
Not completed	0	0
Withdrawal of consent (not due to AE)	-	-

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: 125 subjects were enrolled in the Parts DEF. 2 subjects were dosed in the run-in period in Part E, but never got dosed in TC period. 1 subject in Part F was randomized but never dosed in TC period. Therefore, 122 over the total of 125 enrolled subjects entered the TC period.

Baseline characteristics

Reporting groups

Reporting group title	Part D: Placebo
Reporting group description: Subjects received placebo matched to VX-445/TEZ/IVA triple combination (TC) for 4 weeks in the TC treatment period.	
Reporting group title	Part D: VX-445/TEZ/IVA TC - Low Dose
Reporting group description: Subjects received VX-445/TEZ/IVA TC low dose for 4 weeks in the TC treatment period.	
Reporting group title	Part D: VX-445/TEZ/IVA TC - Medium Dose
Reporting group description: Subjects received VX-445/TEZ/IVA TC medium dose for 4 weeks in the TC treatment period.	
Reporting group title	Part D: VX-445/TEZ/IVA TC - High Dose
Reporting group description: Subjects received VX-445/TEZ/IVA TC high dose for 4 weeks in the TC treatment period.	
Reporting group title	Part E: TEZ/IVA
Reporting group description: Following run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA and placebo matched to VX-445 for 4 weeks in the TC treatment period.	
Reporting group title	Part E: VX-445/TEZ/IVA TC
Reporting group description: Following run-in period of 4 weeks with TEZ/IVA, subjects received VX-445/TEZ/IVA for 4 weeks in the TC treatment period.	
Reporting group title	Part F: Placebo
Reporting group description: Subjects received placebo matched to VX-445/TEZ/VX-561 for 4 weeks in the TC treatment period.	
Reporting group title	Part F: VX-445/TEZ/VX-561 TC
Reporting group description: Subjects received VX-445/TEZ/VX-561 TC for 4 weeks in the TC treatment period.	

Reporting group values	Part D: Placebo	Part D: VX-445/TEZ/IVA TC - Low Dose	Part D: VX-445/TEZ/IVA TC - Medium Dose
Number of subjects	12	10	22
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	29.7 ± 7.5	27.1 ± 7.4	31.8 ± 8.3
Gender categorical Units: Subjects			
Female	2	6	7
Male	10	4	15

Reporting group values	Part D: VX-445/TEZ/IVA TC - High Dose	Part E: TEZ/IVA	Part E: VX-445/TEZ/IVA TC
Number of subjects	21	7	21

Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	33.3 ± 10.3	27.9 ± 8.0	29.9 ± 7.6
Gender categorical Units: Subjects			
Female	11	1	9
Male	10	6	12

Reporting group values	Part F: Placebo	Part F: VX-445/TEZ/VX-561 TC	Total
Number of subjects	8	21	122
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	27.8 ± 5.2	30.6 ± 9.5	-
Gender categorical Units: Subjects			
Female	5	10	51
Male	3	11	71

End points

End points reporting groups

Reporting group title	Part D: Placebo
Reporting group description: Subjects received placebo matched to VX-445/TEZ/IVA triple combination (TC) for 4 weeks in the TC treatment period.	
Reporting group title	Part D: VX-445/TEZ/IVA TC - Low Dose
Reporting group description: Subjects received VX-445/TEZ/IVA TC low dose for 4 weeks in the TC treatment period.	
Reporting group title	Part D: VX-445/TEZ/IVA TC - Medium Dose
Reporting group description: Subjects received VX-445/TEZ/IVA TC medium dose for 4 weeks in the TC treatment period.	
Reporting group title	Part D: VX-445/TEZ/IVA TC - High Dose
Reporting group description: Subjects received VX-445/TEZ/IVA TC high dose for 4 weeks in the TC treatment period.	
Reporting group title	Part E: TEZ/IVA
Reporting group description: Following run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA and placebo matched to VX-445 for 4 weeks in the TC treatment period.	
Reporting group title	Part E: VX-445/TEZ/IVA TC
Reporting group description: Following run-in period of 4 weeks with TEZ/IVA, subjects received VX-445/TEZ/IVA for 4 weeks in the TC treatment period.	
Reporting group title	Part F: Placebo
Reporting group description: Subjects received placebo matched to VX-445/TEZ/VX-561 for 4 weeks in the TC treatment period.	
Reporting group title	Part F: VX-445/TEZ/VX-561 TC
Reporting group description: Subjects received VX-445/TEZ/VX-561 TC for 4 weeks in the TC treatment period.	

Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
End point description: The number of subjects analysed included only subjects who received at least one dose of study drug in the TC treatment period.	
End point type	Primary
End point timeframe: From first dose of study drug in TC treatment period up to 28 days after last dose of study drug	

Notes:

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

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

End point values	Part D: Placebo	Part D: VX-445/TEZ/IVA TC - Low Dose	Part D: VX-445/TEZ/IVA TC - Medium Dose	Part D: VX-445/TEZ/IVA TC - High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10	22	21
Units: Subjects				
Subjects with AEs	12	10	21	18
Subjects with SAEs	2	1	2	0

End point values	Part E: TEZ/IVA	Part E: VX-445/TEZ/IVA TC	Part F: Placebo	Part F: VX-445/TEZ/VX-561 TC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	21	8	21
Units: Subjects				
Subjects with AEs	5	19	7	19
Subjects with SAEs	1	0	1	0

Statistical analyses

No statistical analyses for this end point

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

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) ^[2]
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End point description:

The number of subjects analysed included all randomized subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug in the TC treatment period.

End point type	Primary
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End point timeframe:

From Baseline through Day 29

Notes:

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

Justification: The study was designed to perform within treatment group comparisons. Because only between treatment comparisons can be reported in the EudraCT database, no statistical analyses are reported.

End point values	Part D: Placebo	Part D: VX-445/TEZ/IVA TC - Low Dose	Part D: VX-445/TEZ/IVA TC - Medium Dose	Part D: VX-445/TEZ/IVA TC - High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	22	21
Units: Percentage points				
least squares mean (standard error)	0.0 (± 2.0)	11.1 (± 2.1)	7.9 (± 1.4)	13.8 (± 1.4)

End point values	Part E: TEZ/IVA	Part E: VX- 445/TEZ/IVA TC	Part F: Placebo	Part F: VX- 445/TEZ/VX- 561 TC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	21	8	21
Units: Percentage points				
least squares mean (standard error)	0.4 (± 2.8)	11.0 (± 1.5)	1.2 (± 2.6)	11.7 (± 1.6)

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Part D: Placebo
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Reporting group description:

Subjects received placebo matched to VX-445/TEZ/IVA TC for 4 weeks in the TC treatment period.

Reporting group title	Part D: VX-445/TEZ/IVA TC - Low Dose
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Reporting group description:

Subjects received VX-445/TEZ/IVA TC low dose for 4 weeks in the TC treatment period.

Reporting group title	Part D: VX-445/TEZ/IVA TC - Medium Dose
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Reporting group description:

Subjects received VX-445/TEZ/IVA TC medium dose for 4 weeks in the TC treatment period.

Reporting group title	Part D: VX-445/TEZ/IVA TC - High Dose
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Reporting group description:

Subjects received VX-445/TEZ/IVA TC high dose for 4 weeks in the TC treatment period.

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

Following run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA and placebo matched to VX-445 for 4 weeks in the TC treatment period.

Reporting group title	Part E: VX-445/TEZ/IVA TC
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Reporting group description:

Following run-in period of 4 weeks with TEZ/IVA, subjects received VX-445/TEZ/IVA TC for 4 weeks in the TC treatment period.

Reporting group title	Part F: Placebo
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Reporting group description:

Subjects received placebo matched to VX-445/TEZ/VX-561 TC for 4 weeks in the TC treatment period.

Reporting group title	Part F: VX-445/TEZ/VX-561 TC
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Reporting group description:

Subjects with CF received VX-445/TEZ/VX-561 TC for 4 weeks in the TC treatment period.

Serious adverse events	Part D: Placebo	Part D: VX-445/TEZ/IVA TC - Low Dose	Part D: VX-445/TEZ/IVA TC - Medium Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	1 / 10 (10.00%)	2 / 22 (9.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Influenza A virus test positive			

subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 10 (10.00%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part D: VX-445/TEZ/IVA TC - High Dose	Part E: TEZ/IVA	Part E: VX-445/TEZ/IVA TC
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Influenza A virus test positive			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part F: Placebo	Part F: VX-445/TEZ/VX-561 TC	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Influenza A virus test positive			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Jugular vein thrombosis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (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 D: Placebo	Part D: VX-445/TEZ/IVA TC - Low Dose	Part D: VX-445/TEZ/IVA TC - Medium Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	10 / 10 (100.00%)	19 / 22 (86.36%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 12 (33.33%)	1 / 10 (10.00%)	0 / 22 (0.00%)
occurrences (all)	4	1	0
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	5 / 22 (22.73%)
occurrences (all)	1	0	5
Malaise			

subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	4 / 10 (40.00%)	5 / 22 (22.73%)
occurrences (all)	1	4	6
Sputum increased			
subjects affected / exposed	3 / 12 (25.00%)	3 / 10 (30.00%)	4 / 22 (18.18%)
occurrences (all)	3	4	4
Haemoptysis			
subjects affected / exposed	2 / 12 (16.67%)	0 / 10 (0.00%)	5 / 22 (22.73%)
occurrences (all)	3	0	9
Oropharyngeal pain			
subjects affected / exposed	2 / 12 (16.67%)	2 / 10 (20.00%)	2 / 22 (9.09%)
occurrences (all)	2	2	2
Nasal congestion			
subjects affected / exposed	2 / 12 (16.67%)	2 / 10 (20.00%)	2 / 22 (9.09%)
occurrences (all)	3	2	2
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	2
Sinus congestion			

subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	1 / 22 (4.55%)
occurrences (all)	0	1	2
Productive cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiration abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Sputum discoloured			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Paranasal sinus discomfort			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	3 / 22 (13.64%)
occurrences (all)	0	0	3
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Pleuritic pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Bronchiectasis			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Pulmonary mass subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	1 / 22 (4.55%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Forced expiratory volume decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Blood triglycerides increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Pulmonary function test decreased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Injury, poisoning and procedural complications Radiation injury subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0

Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)	2 / 10 (20.00%)	2 / 22 (9.09%)
occurrences (all)	2	2	2
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 10 (10.00%)	3 / 22 (13.64%)
occurrences (all)	1	1	3
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	2 / 10 (20.00%)	3 / 22 (13.64%)
occurrences (all)	3	2	3
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 10 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 10 (10.00%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Abdominal discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 10 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0

Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 10 (10.00%) 1	0 / 22 (0.00%) 0
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Acne subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 10 (20.00%) 2	0 / 22 (0.00%) 0
Pruritus generalised subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	1 / 22 (4.55%) 2
Neck pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 10 (0.00%) 0	0 / 22 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 10 (10.00%) 1	0 / 22 (0.00%) 0

Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Catheter site infection subjects affected / exposed occurrences (all) Gastroenteritis viral subjects affected / exposed occurrences (all) Otitis media subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 4 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	2 / 10 (20.00%) 2 1 / 10 (10.00%) 2 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	4 / 22 (18.18%) 4 0 / 22 (0.00%) 0 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 10 (10.00%) 1	0 / 22 (0.00%) 0
Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 10 (10.00%) 1	0 / 22 (0.00%) 0

Non-serious adverse events	Part D: VX-445/TEZ/IVA TC - High Dose	Part E: TEZ/IVA	Part E: VX-445/TEZ/IVA TC
Total subjects affected by non-serious adverse events subjects affected / exposed	17 / 21 (80.95%)	5 / 7 (71.43%)	18 / 21 (85.71%)
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	4 / 21 (19.05%) 4
Pyrexia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 7 (14.29%) 1	3 / 21 (14.29%) 3
Malaise subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	1 / 21 (4.76%) 1
Pain subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 7 (14.29%) 1	1 / 21 (4.76%) 1
Chest pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	1 / 21 (4.76%) 1
Chills subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	3 / 21 (14.29%) 3
Chest discomfort subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough			

subjects affected / exposed	7 / 21 (33.33%)	1 / 7 (14.29%)	7 / 21 (33.33%)
occurrences (all)	9	1	8
Sputum increased			
subjects affected / exposed	5 / 21 (23.81%)	0 / 7 (0.00%)	8 / 21 (38.10%)
occurrences (all)	7	0	10
Haemoptysis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 7 (0.00%)	3 / 21 (14.29%)
occurrences (all)	4	0	4
Oropharyngeal pain			
subjects affected / exposed	2 / 21 (9.52%)	1 / 7 (14.29%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Nasal congestion			
subjects affected / exposed	2 / 21 (9.52%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	1 / 21 (4.76%)	1 / 7 (14.29%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Respiration abnormal			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Sputum discoloured			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Paranasal sinus discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Lower respiratory tract congestion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pleuritic pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Bronchiectasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pulmonary mass			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 21 (9.52%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	4 / 21 (19.05%)
occurrences (all)	1	0	4
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	3 / 21 (14.29%)
occurrences (all)	1	0	3
Forced expiratory volume decreased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Blood triglycerides increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pulmonary function test decreased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Radiation injury			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Dizziness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 21 (4.76%)	1 / 7 (14.29%)	1 / 21 (4.76%)
occurrences (all)	1	1	2
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 21 (4.76%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Abdominal discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pruritus generalised			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 7 (14.29%) 1	0 / 21 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	1 / 7 (14.29%) 1	1 / 21 (4.76%) 1
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2	0 / 7 (0.00%) 0	5 / 21 (23.81%) 6
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 4	1 / 7 (14.29%) 1	1 / 21 (4.76%) 1
Sinusitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 7 (0.00%) 0	0 / 21 (0.00%) 0
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	0 / 7 (0.00%) 0	1 / 21 (4.76%) 1
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Catheter site infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 21 (0.00%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 7 (14.29%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 7 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Part F: Placebo	Part F: VX-445/TEZ/VX-561 TC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	17 / 21 (80.95%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Malaise			

subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Chest discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 8 (25.00%)	5 / 21 (23.81%)	
occurrences (all)	2	5	
Sputum increased			
subjects affected / exposed	1 / 8 (12.50%)	3 / 21 (14.29%)	
occurrences (all)	1	4	
Haemoptysis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 8 (25.00%)	5 / 21 (23.81%)	
occurrences (all)	2	5	
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Sinus congestion			

subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	2
Paranasal sinus hypersecretion		
subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	1
Productive cough		
subjects affected / exposed	1 / 8 (12.50%)	2 / 21 (9.52%)
occurrences (all)	2	3
Respiration abnormal		
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	1	0
Sputum discoloured		
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)
occurrences (all)	1	1
Paranasal sinus discomfort		
subjects affected / exposed	0 / 8 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	2
Rhinorrhoea		
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0
Epistaxis		
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)
occurrences (all)	1	0
Wheezing		
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0
Lower respiratory tract congestion		
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0
Pleuritic pain		
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0
Upper-airway cough syndrome		
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0
Bronchiectasis		

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 21 (0.00%) 0	
Pulmonary mass subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Investigations Blood bilirubin increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 21 (4.76%) 1	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 21 (4.76%) 1	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 21 (4.76%) 1	
Forced expiratory volume decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 21 (4.76%) 1	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Blood triglycerides increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Pulmonary function test decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Injury, poisoning and procedural complications Radiation injury subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	3 / 8 (37.50%)	2 / 21 (9.52%)	
occurrences (all)	6	3	
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	

Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 21 (0.00%) 0	
Acne subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 21 (4.76%) 1	
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Eczema subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 21 (0.00%) 0	
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 21 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Neck pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 21 (0.00%) 0	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 21 (0.00%) 0	

<p>Infections and infestations</p> <p>Infective pulmonary exacerbation of cystic fibrosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sinusitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oral candidiasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Viral upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Catheter site infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis viral</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Otitis media</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tonsillitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Viral infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 8 (37.50%)</p> <p>4</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>1 / 8 (12.50%)</p> <p>1</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p> <p>0 / 8 (0.00%)</p> <p>0</p>	<p>3 / 21 (14.29%)</p> <p>3</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>1 / 21 (4.76%)</p> <p>1</p> <p>2 / 21 (9.52%)</p> <p>2</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p> <p>0 / 21 (0.00%)</p> <p>0</p>	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	
Hypoglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 21 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2017	- Revised study design to include Parts D and E
28 June 2017	- Updated eligibility criteria, revised data analysis plans, defined dose levels for parts D and E
08 August 2017	- Revised study design to include Part F

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported