Clinical trial results:
A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for F508del and a Minimal Function Mutation (F/MF)

Summary

EudraCT number	2021-000712-31
Trial protocol	SE DE CZ IE ES PT HU
Global end of trial date	21 November 2023

Results information

Result version number	v1 (current)
This version publication date	26 May 2024
First version publication date	26 May 2024

Trial information

Trial identification

Sponsor protocol code	VX20-121-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05033080
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-003052-PIP01-21
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	14 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 May 2023
Global end of trial reached?	Yes
Global end of trial date	21 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-121/tezacaftor/deutivacaftor (VX-121/TEZ/D-IVA) in cystic fibrosis (CF) subjects who are heterozygous for 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 Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2021
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	Ireland: 7
Country: Number of subjects enrolled	United States: 199
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	New Zealand: 17
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Portugal: 8
Country: Number of subjects enrolled	Czechia: 6
Worldwide total number of subjects	435
EEA total number of subjects	141

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)	61
Adults (18-64 years)	372
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in cystic fibrosis (CF) subjects aged 12 years or older. It was pre-specified in the protocol to combine the data from this study with study VX20-121-103 (NCT05076149) for selected endpoints.

Pre-assignment

Screening details:

A total of 435 subjects were enrolled in this study, of which 37 were included in the run-in period but were not dosed in treatment period. Therefore, results are presented for only 398 subjects dosed in the treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ELX/TEZ/IVA

Arm description:

Following elexacftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) run-in period of 4 weeks, subjects received ELX 200 milligram (mg) once daily (qd) /TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 52 weeks.

Arm type	Active comparator
Investigational medicinal product name	ELX/TEZ/IVA
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	Elexacaftor/Tezacaftor/Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination (FDC) 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	VX-121/TEZ/D-IVA

Arm description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	VX-121/TEZ/D-IVA
Investigational medicinal product code	VX-121/VX-661/VX-561
Other name	VX-121/tezacaftor/deutivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-121/TEZ/D-IVA fixed-dose combination (FDC) once daily in the morning.

Number of subjects in period 1[1]	ELX/TEZ/IVA	VX-121/TEZ/D-IVA
Started	202	196
Completed	191	184
Not completed	11	12
Physician decision	-	1
Other	1	1
Adverse event	4	4
Lost to follow-up	1	-
Other non-compliance	-	1
Withdrawal of consent (not due to AE)	5	5

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: A total of 435 subjects were enrolled in the study, of which 37 were included in the run-in period but were not dosed in treatment period. Therefore, results are presented for only 398 subjects dosed in the treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Following elexacftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) run-in period of 4 weeks, subjects received ELX 200 milligram (mg) once daily (qd) /TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 52 weeks.	
Reporting group title	VX-121/TEZ/D-IVA
Reporting group description:	
Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.	

Reporting group values	ELX/TEZ/IVA	VX-121/TEZ/D-IVA	Total
Number of subjects	202	196	398
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	30.9	30.8	
standard deviation	± 11.4	± 10.5	-
Gender categorical			
Units: Subjects			
Female	83	80	163
Male	119	116	235
Race			
Units: Subjects			
Hispanic or Latino	11	13	24
Not Hispanic or Latino	190	183	373
Not Collected per Local Regulations	1	0	1
Ethnicity			
Units: Subjects			
White	197	191	388
Black or African American	1	4	5
Asian	0	1	1
Other	1	0	1
More than one race	3	0	3
Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)			
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.			
Units: Percentage points			
arithmetic mean	67.2	67.0	
standard deviation	± 14.6	± 15.3	-

End points

End points reporting groups

Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Following elexacftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) run-in period of 4 weeks, subjects received ELX 200 milligram (mg) once daily (qd) /TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 52 weeks.	
Reporting group title	VX-121/TEZ/D-IVA
Reporting group description:	
Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.	

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. The Full Analysis Set (FAS) included all all randomized subjects who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. Here " Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.	
End point type	Primary
End point timeframe:	
From Baseline Through Week 24	

End point values	ELX/TEZ/IVA	VX-121/TEZ/D-IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	187		
Units: percentage points				
least squares mean (confidence interval 95%)	0.3 (-0.3 to 0.9)	0.5 (-0.1 to 1.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ELX/TEZ/IVA v VX-121/TEZ/D-IVA
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.1

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	ELX/TEZ/IVA	VX-121/TEZ/D-IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	185		
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	0.9 (-0.6 to 2.3)	-7.5 (-9.0 to -6.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ELX/TEZ/IVA v VX-121/TEZ/D-IVA
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	-6.3

Secondary: Percentage of Subjects With SwCl <60 mmol/L (Pooled With Data From Study VX20-121-103)

End point title	Percentage of Subjects With SwCl <60 mmol/L (Pooled With

	Data From Study VX20-121-103)

End point description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-102) and from Study VX20-121-103 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point. Here "n" signifies pooled analysis subjects who were evaluable at specified time points for each reporting group respectively.

End point type	Secondary

End point timeframe:

From Baseline Through Week 24

End point values	ELX/TEZ/IVA	VX-121/TEZ/D-IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[1]	196[2]		
Units: percentage of subjects				
number (not applicable)				
n=491,480	76.6	85.8		

Notes:

[1] - Out of 491 subjects, 202 subjects were enrolled in the 121–102 and 289 subjects in the 121–103 study
[2] - Out of 491 subjects, 196 subjects were enrolled in the 121–102 and 284 subjects in the 121–103 study

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	VX-121/TEZ/D-IVA v ELX/TEZ/IVA
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Generalized Estimated Equation Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.55
upper limit	3.15

Secondary: Percentage of Subjects With SwCl <30 mmol/L (Pooled With Data From Study VX20-121-103)

End point title	Percentage of Subjects With SwCl <30 mmol/L (Pooled With Data From Study VX20-121-103)

End point description:

PFAS. Here " Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point. Here "n" signifies pooled analysis subjects who were evaluable at specified time points for each reporting group respectively.

End point type	Secondary

End point timeframe:

From Baseline Through Week 24

End point values	ELX/TEZ/IVA	VX-121/TEZ/D-IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[3]	196[4]		
Units: percentage of subjects				
number (not applicable)				
n=491,480	22.5	30.5		

Notes:

[3] - Out of 491 subjects, 202 subjects were enrolled in the 121–102 and 289 subjects in the 121–103 study

[4] - Out of 480 subjects, 196 subjects were enrolled in the 121–102 and 284 subjects in the 121–103 study

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ELX/TEZ/IVA v VX-121/TEZ/D-IVA
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Generalized Estimated Equation Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	4.12

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Safety follow-up (up to 56 weeks)

Adverse event reporting additional description:

Safety set include all subjects who received at least 1 dose of study drug during the Treatment Period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	ELX/TEZ/IVA

Reporting group description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 52 weeks.

Reporting group title	VX-121/TEZ/D-IVA

Reporting group description:

Following ELX/TEZ/IVA run-in period of 4 weeks, subjects received VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd in the treatment period for 52 weeks.

Serious adverse events	ELX/TEZ/IVA	VX-121/TEZ/D-IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 202 (20.30%)	28 / 196 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			

subjects affected / exposed	2 / 202 (0.99%)	2 / 196 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression suicidal			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed anxiety and depressive disorder			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 202 (0.50%)	2 / 196 (1.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behaviour disorder			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 202 (0.99%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (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			
Postoperative ileus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (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			
Cerebrovascular arteriovenous malformation			

subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serotonin syndrome			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 202 (0.00%)	2 / 196 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 202 (0.99%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (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	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (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 / 202 (0.50%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	23 / 202 (11.39%)	11 / 196 (5.61%)	
occurrences causally related to treatment / all	0 / 27	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 202 (0.50%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 202 (1.49%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 202 (0.00%)	2 / 196 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 202 (0.50%)	0 / 196 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 202 (0.50%)	3 / 196 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral myocarditis			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperphosphatasaemia			
subjects affected / exposed	0 / 202 (0.00%)	1 / 196 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ELX/TEZ/IVA	VX-121/TEZ/D-IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 202 (91.09%)	177 / 196 (90.31%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	23 / 202 (11.39%)	18 / 196 (9.18%)	
occurrences (all)	27	22	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 202 (3.96%)	12 / 196 (6.12%)	
occurrences (all)	10	15	
Alanine aminotransferase increased			
subjects affected / exposed	10 / 202 (4.95%)	13 / 196 (6.63%)	
occurrences (all)	11	17	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 202 (10.89%)	25 / 196 (12.76%)	
occurrences (all)	40	32	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	21 / 202 (10.40%)	24 / 196 (12.24%)	
occurrences (all)	30	27	
Fatigue			
subjects affected / exposed	16 / 202 (7.92%)	18 / 196 (9.18%)	
occurrences (all)	21	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 202 (6.93%)	10 / 196 (5.10%)	
occurrences (all)	18	11	
Abdominal distension			
subjects affected / exposed	10 / 202 (4.95%)	5 / 196 (2.55%)	
occurrences (all)	11	5	
Abdominal pain upper			
subjects affected / exposed	6 / 202 (2.97%)	12 / 196 (6.12%)	
occurrences (all)	9	14	
Nausea			
subjects affected / exposed	17 / 202 (8.42%)	7 / 196 (3.57%)	
occurrences (all)	20	7	
Diarrhoea			
subjects affected / exposed	15 / 202 (7.43%)	21 / 196 (10.71%)	
occurrences (all)	15	30	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 202 (20.30%)	45 / 196 (22.96%)	
occurrences (all)	57	59	
Productive cough			
subjects affected / exposed	5 / 202 (2.48%)	12 / 196 (6.12%)	
occurrences (all)	7	12	
Haemoptysis			
subjects affected / exposed	10 / 202 (4.95%)	13 / 196 (6.63%)	
occurrences (all)	15	16	
Nasal congestion			
subjects affected / exposed	24 / 202 (11.88%)	19 / 196 (9.69%)	
occurrences (all)	30	25	
Oropharyngeal pain			

subjects affected / exposed	23 / 202 (11.39%)	24 / 196 (12.24%)	
occurrences (all)	29	34	
Sputum increased			
subjects affected / exposed	21 / 202 (10.40%)	18 / 196 (9.18%)	
occurrences (all)	28	24	
Sinus congestion			
subjects affected / exposed	5 / 202 (2.48%)	14 / 196 (7.14%)	
occurrences (all)	8	21	
Rhinorrhoea			
subjects affected / exposed	14 / 202 (6.93%)	19 / 196 (9.69%)	
occurrences (all)	18	25	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 202 (4.46%)	12 / 196 (6.12%)	
occurrences (all)	10	16	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 202 (7.92%)	9 / 196 (4.59%)	
occurrences (all)	18	11	
Arthralgia			
subjects affected / exposed	11 / 202 (5.45%)	10 / 196 (5.10%)	
occurrences (all)	14	11	
Infections and infestations			
COVID-19			
subjects affected / exposed	53 / 202 (26.24%)	49 / 196 (25.00%)	
occurrences (all)	54	53	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	64 / 202 (31.68%)	53 / 196 (27.04%)	
occurrences (all)	114	70	
Influenza			
subjects affected / exposed	10 / 202 (4.95%)	17 / 196 (8.67%)	
occurrences (all)	10	17	
Nasopharyngitis			
subjects affected / exposed	35 / 202 (17.33%)	45 / 196 (22.96%)	
occurrences (all)	63	74	
Viral upper respiratory tract infection			

subjects affected / exposed	18 / 202 (8.91%)	17 / 196 (8.67%)	
occurrences (all)	22	19	
Upper respiratory tract infection			
subjects affected / exposed	27 / 202 (13.37%)	17 / 196 (8.67%)	
occurrences (all)	35	24	
Sinusitis			
subjects affected / exposed	10 / 202 (4.95%)	10 / 196 (5.10%)	
occurrences (all)	13	12	
Respiratory tract infection			
subjects affected / exposed	12 / 202 (5.94%)	8 / 196 (4.08%)	
occurrences (all)	21	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported