

**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 Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation

Summary

EudraCT number	2021-000694-85
Trial protocol	NO SE DE DK IE IT GR BE AT NL PL HU
Global end of trial date	30 November 2023

Results information

Result version number	v1 (current)
This version publication date	01 June 2024
First version publication date	01 June 2024

Trial information**Trial identification**

Sponsor protocol code	VX20-121-103
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05076149
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-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	15 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2023
Global end of trial reached?	Yes
Global end of trial date	30 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 homozygous for F508del, heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other triple combination responsive (TCR) CFTR mutation and no F508del mutation

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	27 October 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	Netherlands: 13
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	New Zealand: 25

Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	United States: 202
Country: Number of subjects enrolled	United Kingdom: 34
Worldwide total number of subjects	597
EEA total number of subjects	266

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)	82
Adults (18-64 years)	513
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 VX20-121-102 (NCT05033080) for selected endpoints.

Pre-assignment

Screening details:

A total of 597 subjects were enrolled in this study, of which 24 were included in the run-in period but were not dosed in treatment period. Therefore, results are presented for only 573 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	Elxacaftor/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	289	284
Completed	279	264
Not completed	10	20
Physician decision	-	1
Other non compliance	1	1
Adverse Event	3	9
Other	5	4
Lost to follow-up	-	1
Withdrawal of consent (not due to AE)	1	3
Commercial drug is available for subject	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 597 subjects were enrolled in the study, of which 24 were included in the run-in period but were not dosed in treatment period. Therefore, results are presented for only 573 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	289	284	573
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	34.0	33.3	
standard deviation	± 12.4	± 12.6	-
Gender categorical			
Units: Subjects			
Female	145	135	280
Male	144	149	293
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	4	9
Not Hispanic or Latino	261	265	526
Not Collected per Local Regulations	23	15	38
Race			
Units: Subjects			
White	262	270	532
Asian	1	1	2
American Indian or Alaska Native	1	0	1
Other	1	1	2
Not Collected per Local Regulations	23	10	33
More than one race	1	2	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	66.4	67.2	
standard deviation	± 14.9	± 14.6	-

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.

Subject analysis set title	ELX/TEZ/IVA (pooled analysis with 121-102)
----------------------------	--

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-103) and from Study VX20-121-102 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints.

Subject analysis set title	VX-121/TEZ/D-IVA (pooled analysis with 121-102)
----------------------------	---

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-103) and from Study VX20-121-102 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints.

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

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1second (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) 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	276	268		
Units: percentage points				
least squares mean (confidence interval 95%)	0.0 (-0.5 to 0.5)	0.2 (-0.3 to 0.7)		

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	544
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	-0.5
upper limit	0.9

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	276	270		
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-2.3 (-3.6 to -0.9)	-5.1 (-6.4 to -3.7)		

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	546
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	-0.9

Secondary: Percentage of subjects with SwCl <60 mmol/L (pooled with data from Study VX20-121-102)

End point title	Percentage of subjects with SwCl <60 mmol/L (pooled with data from Study VX20-121-102)
-----------------	--

End point description:

The Pooled Full Analysis Set (PFAS) included all randomized subjects from this study (VX20-121-103) and from Study VX20-121-102 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS will be used only for pooled analysis of selected endpoints. Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.

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

End point timeframe:

From Baseline Through Week 24

End point values	ELX/TEZ/IVA (pooled analysis with 121-102)	VX-121/TEZ/D- IVA (pooled analysis with 121-102)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	479	465		
Units: percentage of subjects				
number (not applicable)	76.6	85.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ELX/TEZ/IVA (pooled analysis with 121-102) v VX-121/TEZ/D-IVA (pooled analysis with 121-102)
Number of subjects included in analysis	944
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 VX20-121-102)

End point title	Percentage of subjects with SwCl <30 mmol/L (pooled with data from Study VX20-121-102)
-----------------	--

End point description:

PFAS. The PFAS will be used only for pooled analysis of selected endpoints. Here "Number of Subjects Analyzed" signifies those subjects who were evaluated for this specific end point.

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

End point timeframe:

From Baseline Through Week 24

End point values	ELX/TEZ/IVA (pooled analysis with 121-102)	VX-121/TEZ/D- IVA (pooled analysis with 121-102)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	479	465		
Units: percentage of subjects				
number (not applicable)	22.5	30.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	ELX/TEZ/IVA (pooled analysis with 121-102) v VX-121/TEZ/D-IVA (pooled analysis with 121-102)
Number of subjects included in analysis	944
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 52 weeks)

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, participants 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	40 / 289 (13.84%)	40 / 284 (14.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Intermenstrual bleeding			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal cyst			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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 / 289 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute stress disorder			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device leakage			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 289 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 289 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			

subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 289 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural haematoma subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders Seizure subjects affected / exposed	1 / 289 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic headache subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Leukocytosis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatic cyst			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			
subjects affected / exposed	2 / 289 (0.69%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Fatty liver alcoholic			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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	2 / 289 (0.69%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 289 (0.69%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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			
Metapneumovirus pneumonia			

subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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	2 / 289 (0.69%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	12 / 289 (4.15%)	18 / 284 (6.34%)	
occurrences causally related to treatment / all	0 / 13	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 289 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 289 (2.08%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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			
Type 3 diabetes mellitus			
subjects affected / exposed	0 / 289 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 289 (0.35%)	0 / 284 (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	ELX/TEZ/IVA	VX-121/TEZ/D-IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	253 / 289 (87.54%)	252 / 284 (88.73%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	17 / 289 (5.88%)	24 / 284 (8.45%)	
occurrences (all)	18	27	
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 289 (6.23%)	19 / 284 (6.69%)	
occurrences (all)	20	20	
Alanine aminotransferase increased			

subjects affected / exposed occurrences (all)	18 / 289 (6.23%) 22	24 / 284 (8.45%) 25	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	41 / 289 (14.19%) 98	51 / 284 (17.96%) 60	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	29 / 289 (10.03%) 38 30 / 289 (10.38%) 40	28 / 284 (9.86%) 43 33 / 284 (11.62%) 38	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	23 / 289 (7.96%) 30 19 / 289 (6.57%) 23 44 / 289 (15.22%) 49 19 / 289 (6.57%) 24 13 / 289 (4.50%) 14	15 / 284 (5.28%) 18 15 / 284 (5.28%) 18 37 / 284 (13.03%) 46 12 / 284 (4.23%) 14 22 / 284 (7.75%) 23	
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	37 / 289 (12.80%) 50 19 / 289 (6.57%) 24	45 / 284 (15.85%) 58 16 / 284 (5.63%) 24	

Rhinorrhoea			
subjects affected / exposed	22 / 289 (7.61%)	16 / 284 (5.63%)	
occurrences (all)	25	19	
Sinus congestion			
subjects affected / exposed	10 / 289 (3.46%)	18 / 284 (6.34%)	
occurrences (all)	10	25	
Sputum increased			
subjects affected / exposed	29 / 289 (10.03%)	27 / 284 (9.51%)	
occurrences (all)	38	30	
Nasal congestion			
subjects affected / exposed	23 / 289 (7.96%)	29 / 284 (10.21%)	
occurrences (all)	29	36	
Haemoptysis			
subjects affected / exposed	22 / 289 (7.61%)	16 / 284 (5.63%)	
occurrences (all)	36	23	
Dyspnoea			
subjects affected / exposed	21 / 289 (7.27%)	11 / 284 (3.87%)	
occurrences (all)	21	14	
Cough			
subjects affected / exposed	60 / 289 (20.76%)	63 / 284 (22.18%)	
occurrences (all)	88	94	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 289 (4.50%)	25 / 284 (8.80%)	
occurrences (all)	15	30	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 289 (2.08%)	16 / 284 (5.63%)	
occurrences (all)	7	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 289 (8.65%)	14 / 284 (4.93%)	
occurrences (all)	26	15	
Back pain			
subjects affected / exposed	15 / 289 (5.19%)	16 / 284 (5.63%)	
occurrences (all)	15	20	

Infections and infestations			
COVID-19			
subjects affected / exposed	72 / 289 (24.91%)	57 / 284 (20.07%)	
occurrences (all)	79	60	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	85 / 289 (29.41%)	70 / 284 (24.65%)	
occurrences (all)	125	109	
Influenza			
subjects affected / exposed	14 / 289 (4.84%)	29 / 284 (10.21%)	
occurrences (all)	14	30	
Nasopharyngitis			
subjects affected / exposed	60 / 289 (20.76%)	57 / 284 (20.07%)	
occurrences (all)	119	84	
Viral upper respiratory tract infection			
subjects affected / exposed	17 / 289 (5.88%)	20 / 284 (7.04%)	
occurrences (all)	19	26	
Upper respiratory tract infection			
subjects affected / exposed	40 / 289 (13.84%)	55 / 284 (19.37%)	
occurrences (all)	59	71	
Sinusitis			
subjects affected / exposed	26 / 289 (9.00%)	9 / 284 (3.17%)	
occurrences (all)	31	11	

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