Clinical trial results:
A Phase 3, Open-label Study Evaluating the Long-term Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis

Summary

EudraCT number	2018-004652-38
Trial protocol	IE GB DE DK PL
Global end of trial date	14 December 2022

Results information

Result version number	v1 (current)
This version publication date	30 June 2023
First version publication date	30 June 2023

Trial information

Trial identification

Sponsor protocol code	VX18-445-113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04043806
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)	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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2022
Global end of trial reached?	Yes
Global end of trial date	14 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA)

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	09 August 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	34 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	United States: 243
Country: Number of subjects enrolled	Australia: 46
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Ireland: 23
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	458
EEA total number of subjects	101

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	83
Adults (18-64 years)	375
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted as a single part study (Part A) in countries including United States (US) with commercially available ELX/TEZ/IVA. The regional protocol for countries without commercially available ELX/TEZ/IVA was amended so that subjects in these countries had the opportunity to participate for up to an additional 48 weeks in Part B.

Pre-assignment

Screening details:

A total of 458 subjects were enrolled from the parent study VX17-659-105 (NCT03447262). One subject was enrolled but did not receive any dose in this study.

Period 1

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

Arms

Arm title	Part A: ELX/TEZ/IVA

Arm description:

Subjects received ELX (elexacaftor) 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every
12 hours (q12h) in the treatment period for 96 weeks.

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

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed dose combination once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1[1]	Part A: ELX/TEZ/IVA
Started	457
Completed	412
Not completed	45
Commercial drug is available for subjects	13
Physician decision	2

Other	12
Adverse event	2
Lost to follow-up	6
Other non-compliance	2
Withdrawal of Consent (not due to AE)	8

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 458 subjects were enrolled from the parent studies. One subject in enrolled but not dosed in this study. Therefore, data for 457 subjects are reported in the subject disposition and baseline characteristics sections.

Period 2

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

Arms

Arm title	Part B: ELX/TEZ/IVA

Arm description:

Subjects from certain countries participated in Part B and continued to receive ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.

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

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed dose combination once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 2[2]	Part B: ELX/TEZ/IVA
Started	66
Completed	8
Not completed	58
Commercial drug is available for subjects	51
Other	6
Adverse event	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 458 subjects were enrolled in the parent studies on Part A. However, only 66 subjects rolled over to Part B from Part A of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Part A
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks.	

Reporting group values	Part A	Total	
Number of subjects	457	457	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	28.5		
standard deviation	± 9.8	-	
Gender categorical			
Units: Subjects			
Female	202	202	
Male	255	255	
Ethnicity			
Units: Subjects			
Hispanic or Latino	14	14	
Not Hispanic or Latino	437	437	
Not collected per local regulations	6	6	
Race			
Units: Subjects			
White	445	445	
Black or African American	3	3	
Asian	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Not collected per local regulations	5	5	
Multiple	4	4	

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX (elexacaftor) 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the treatment period for 96 weeks.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects from certain countries participated in Part B and continued to receive ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.	

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

End point title	Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]
End point description:	
Safety set included all subjects who received at least 1 dose of study drug in the treatment period.	
End point type	Primary
End point timeframe:	
From Baseline through Week 100	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	457			
Units: Subjects				
Subjects with TEAEs	435			
Subjects with SAEs	75			

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[2]
End point description:	
Safety set included all subjects who received at least 1 dose of study drug in the treatment period.	
End point type	Primary

End point timeframe:

From Baseline through Week 52

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: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: Subjects				
Subjects with TEAEs	50			
Subjects with SAEs	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 through Safety follow-up (up to Week 100 for Part A and up to Week 52 for Part B)	
Adverse event reporting additional description:	
MedDRA 25.0 for Part A and MedDRA 25.1 for Part B	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0,25.1

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 96 weeks.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects from certain countries participated in Part B and continued to receive ELX 200 mg qd /TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 48 weeks.	

Serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 457 (16.41%)	4 / 66 (6.06%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device occlusion			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (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	3 / 457 (0.66%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Generalised anxiety disorder			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced mood disorder			

subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 457 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	0 / 457 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			
subjects affected / exposed	0 / 457 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 457 (0.22%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural fistula			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site discharge			
subjects affected / exposed	0 / 457 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			
subjects affected / exposed	2 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Piriformis syndrome			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	3 / 457 (0.66%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			

subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (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	2 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (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 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint instability			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (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			
Abdominal abscess			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

COVID-19			
subjects affected / exposed	2 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex pharyngitis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (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 / 457 (0.44%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 457 (1.53%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			

subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	31 / 457 (6.78%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 49	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal loss of weight			
subjects affected / exposed	1 / 457 (0.22%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	404 / 457 (88.40%)	45 / 66 (68.18%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	39 / 457 (8.53%)	0 / 66 (0.00%)	
occurrences (all)	42	0	
Alanine aminotransferase increased			
subjects affected / exposed	39 / 457 (8.53%)	3 / 66 (4.55%)	
occurrences (all)	47	3	
Aspartate aminotransferase increased			
subjects affected / exposed	31 / 457 (6.78%)	3 / 66 (4.55%)	
occurrences (all)	38	3	
Nervous system disorders			
Headache			
subjects affected / exposed	92 / 457 (20.13%)	5 / 66 (7.58%)	
occurrences (all)	145	5	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	63 / 457 (13.79%)	1 / 66 (1.52%)	
occurrences (all)	102	1	
Pain			
subjects affected / exposed	24 / 457 (5.25%)	0 / 66 (0.00%)	
occurrences (all)	34	0	
Fatigue			
subjects affected / exposed	46 / 457 (10.07%)	4 / 66 (6.06%)	
occurrences (all)	60	4	
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	42 / 457 (9.19%)	1 / 66 (1.52%)	
occurrences (all)	75	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	30 / 457 (6.56%)	2 / 66 (3.03%)	
occurrences (all)	41	3	
Diarrhoea			
subjects affected / exposed	33 / 457 (7.22%)	1 / 66 (1.52%)	
occurrences (all)	41	1	
Nausea			
subjects affected / exposed	40 / 457 (8.75%)	2 / 66 (3.03%)	
occurrences (all)	54	2	
Vomiting			
subjects affected / exposed	25 / 457 (5.47%)	6 / 66 (9.09%)	
occurrences (all)	28	6	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	26 / 457 (5.69%)	1 / 66 (1.52%)	
occurrences (all)	33	1	
Cough			
subjects affected / exposed	114 / 457 (24.95%)	6 / 66 (9.09%)	
occurrences (all)	170	7	
Oropharyngeal pain			
subjects affected / exposed	61 / 457 (13.35%)	1 / 66 (1.52%)	
occurrences (all)	89	1	
Haemoptysis			
subjects affected / exposed	41 / 457 (8.97%)	5 / 66 (7.58%)	
occurrences (all)	69	13	
Nasal congestion			
subjects affected / exposed	52 / 457 (11.38%)	0 / 66 (0.00%)	
occurrences (all)	72	0	
Sputum increased			
subjects affected / exposed	67 / 457 (14.66%)	0 / 66 (0.00%)	
occurrences (all)	94	0	
Sinus congestion			
subjects affected / exposed	26 / 457 (5.69%)	0 / 66 (0.00%)	
occurrences (all)	37	0	
Rhinorrhoea			

subjects affected / exposed	36 / 457 (7.88%)	2 / 66 (3.03%)	
occurrences (all)	46	3	
Respiration abnormal			
subjects affected / exposed	24 / 457 (5.25%)	0 / 66 (0.00%)	
occurrences (all)	28	0	
Productive cough			
subjects affected / exposed	27 / 457 (5.91%)	0 / 66 (0.00%)	
occurrences (all)	32	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	26 / 457 (5.69%)	1 / 66 (1.52%)	
occurrences (all)	32	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 457 (5.91%)	2 / 66 (3.03%)	
occurrences (all)	28	2	
Back pain			
subjects affected / exposed	31 / 457 (6.78%)	1 / 66 (1.52%)	
occurrences (all)	36	1	
Myalgia			
subjects affected / exposed	23 / 457 (5.03%)	0 / 66 (0.00%)	
occurrences (all)	27	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	71 / 457 (15.54%)	10 / 66 (15.15%)	
occurrences (all)	107	10	
Sinusitis			
subjects affected / exposed	31 / 457 (6.78%)	3 / 66 (4.55%)	
occurrences (all)	44	3	
Nasopharyngitis			
subjects affected / exposed	61 / 457 (13.35%)	1 / 66 (1.52%)	
occurrences (all)	90	1	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	107 / 457 (23.41%)	12 / 66 (18.18%)	
occurrences (all)	222	15	
COVID-19			

subjects affected / exposed	30 / 457 (6.56%)	18 / 66 (27.27%)	
occurrences (all)	32	18	
Viral upper respiratory tract infection			
subjects affected / exposed	46 / 457 (10.07%)	0 / 66 (0.00%)	
occurrences (all)	56	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2021	Amended to include an optional at-home sweat chloride sample collection; Amended the treatment period by an additional 48 weeks (Part B) to evaluate the safety of ELX/TEZ/IVA beyond 96 weeks of treatment; Amended the study design to provide the opportunity for subjects who depart this study to enroll in another qualified Vertex study of investigational CFTR modulators, but do not receive the first study drug dose in the Treatment Period of the other study, to return to this study (applies to both Part A and Part B); Amended the statistical analysis section to reflect the updated study design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported