Clinical trial results:
A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis (CF) Who Are Homozygous or Heterozygous for the F508del Mutation

Summary

EudraCT number	2018-000185-11
Trial protocol	SE DE GB CZ BE NL AT GR FR IT
Global end of trial date	09 January 2023

Results information

Result version number	v1 (current)
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	VX17-445-105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03525574
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-002324-PIP01-17
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	06 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2023
Global end of trial reached?	Yes
Global end of trial date	09 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who were homozygous or heterozygous for the 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	09 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	56 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	United States: 280
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Netherlands: 32
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	507
EEA total number of subjects	147

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)	145
Adults (18-64 years)	362
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects from the parent studies VX17-445-102 (NCT03525444) and VX17-445-103 (NCT03525548) were enrolled in this study. A total of 507 subjects were enrolled in this study.

Period 1

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

Arms

Arm title	Treatment Period: ELX/TEZ/IVA

Arm description:

Subjects received ELX 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hrs (q12h) in the treatment period for 192 weeks.

Arm type	Experimental
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 VX-445/TEZ/IVA TC, once daily in the morning.

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

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1[1]	Treatment Period: ELX/TEZ/IVA
Started	506
Completed	354
Not completed	152
Physician decision	6
Commercial Drug is Available for Subject	48
Death	1
Other	58
Adverse event	15

Other non-compliance	2
Lost to follow-up	4
Withdrawal of consent (not due to AE)	18

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 507 subjects were enrolled from the parent studies. One subject is enrolled but was not dosed in this study. Therefore, data for 506 subjects are reported in the subject disposition and baseline sections.

Period 2

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

Arms

Arm title	Extension Period: ELX/TEZ/IVA

Arm description:

Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the extension period for 48 weeks.

Arm type	Experimental
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 triple combination (TC), once daily in the morning.

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

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 2[2]	Extension Period: ELX/TEZ/IVA
Started	11
Completed	0
Not completed	11
Commercial Drug is Available for Subject	10
Other	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 507 subjects were enrolled in the parent studies on treatment period. However, only 11 subjects rolled over to extension period from treatment period of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hrs (q12h) in the treatment period for 192 weeks.	

Reporting group values	Treatment Period: ELX/TEZ/IVA	Total	
Number of subjects	506	506	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 26.7 ± 10.7	 -	
Gender categorical Units: Subjects			
Female	251	251	
Male	255	255	

End points

End points reporting groups

Reporting group title	Treatment Period: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 milligram (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hrs (q12h) in the treatment period for 192 weeks.	
Reporting group title	Extension Period: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the extension period for 48 weeks.	

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

End point title	Treatment Period: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1]
End point description:	
The Open-Label Safety Set (OL-SS) included all subjects who had received at least 1 dose of study drug in the OL study.	
End point type	Primary
End point timeframe:	
From Day 1 up to Week 196	

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	Treatment Period: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	506			
Units: subjects				
Subjects With TEAEs	504			
Subjects With SAEs	175			

Statistical analyses

No statistical analyses for this end point

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

End point title	Extension Period: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[2]

End point description:

The Open-label Extension Period Safety Set (OL-EP-SS) include all subjects who have received at least 1 dose of study drug in the Extension Period of the OL study.

End point type	Primary

End point timeframe:

From Day 1 up to 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	Extension Period: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: subjects				
Subjects With TEAEs	7			
Subjects With SAEs	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Safety follow-up (up to Week 196 for Treatment period and up to Week 52 for Extension period)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Treatment Period: 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 192 weeks.	
Reporting group title	Extension Period: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the extension period for 48 weeks.	

Serious adverse events	Treatment Period: ELX/TEZ/IVA	Extension Period: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	175 / 506 (34.58%)	0 / 11 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Philadelphia positive acute lymphocytic leukaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Pyrexia			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Physical deconditioning			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Breast mass			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular torsion			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Dyspnoea			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	11 / 506 (2.17%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	2 / 19	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rales			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sputum increased			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	3 / 506 (0.59%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia nervosa			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anger			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus test positive			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial test positive			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 506 (0.99%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			

subjects affected / exposed	5 / 506 (0.99%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture of penis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site pain			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Cystic fibrosis lung			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis constrictive			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postural orthostatic tachycardia syndrome			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Miller Fisher syndrome			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Optic neuritis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	4 / 506 (0.79%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	6 / 506 (1.19%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	9 / 506 (1.78%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	2 / 25	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric fistula			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	5 / 506 (0.99%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	3 / 506 (0.59%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 506 (0.59%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	5 / 506 (0.99%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Rheumatoid arthritis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	83 / 506 (16.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	3 / 150	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial disease carrier			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	4 / 506 (0.79%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	3 / 506 (0.59%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	7 / 506 (1.38%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	6 / 506 (1.19%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	4 / 506 (0.79%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	3 / 506 (0.59%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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			
Diabetes mellitus inadequate control			

subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 506 (0.40%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 506 (0.20%)	0 / 11 (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	Treatment Period: ELX/TEZ/IVA	Extension Period: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	501 / 506 (99.01%)	7 / 11 (63.64%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	147 / 506 (29.05%)	0 / 11 (0.00%)	
occurrences (all)	235	0	
Pain			
subjects affected / exposed	37 / 506 (7.31%)	0 / 11 (0.00%)	
occurrences (all)	43	0	
Malaise			
subjects affected / exposed	26 / 506 (5.14%)	0 / 11 (0.00%)	
occurrences (all)	42	0	
Influenza like illness			
subjects affected / exposed	33 / 506 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	43	0	
Fatigue			
subjects affected / exposed	118 / 506 (23.32%)	0 / 11 (0.00%)	
occurrences (all)	205	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	45 / 506 (8.89%)	0 / 11 (0.00%)	
occurrences (all)	56	0	
Immunisation reaction			
subjects affected / exposed	83 / 506 (16.40%)	0 / 11 (0.00%)	
occurrences (all)	164	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	231 / 506 (45.65%)	0 / 11 (0.00%)	
occurrences (all)	567	0	
Dyspnoea			
subjects affected / exposed	62 / 506 (12.25%)	0 / 11 (0.00%)	
occurrences (all)	104	0	
Haemoptysis			
subjects affected / exposed	82 / 506 (16.21%)	1 / 11 (9.09%)	
occurrences (all)	188	1	

Lower respiratory tract congestion			
subjects affected / exposed	37 / 506 (7.31%)	0 / 11 (0.00%)	
occurrences (all)	52	0	
Nasal congestion			
subjects affected / exposed	113 / 506 (22.33%)	0 / 11 (0.00%)	
occurrences (all)	184	0	
Oropharyngeal pain			
subjects affected / exposed	166 / 506 (32.81%)	1 / 11 (9.09%)	
occurrences (all)	315	1	
Productive cough			
subjects affected / exposed	61 / 506 (12.06%)	0 / 11 (0.00%)	
occurrences (all)	91	0	
Respiration abnormal			
subjects affected / exposed	33 / 506 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	47	0	
Wheezing			
subjects affected / exposed	33 / 506 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	54	0	
Sputum increased			
subjects affected / exposed	127 / 506 (25.10%)	0 / 11 (0.00%)	
occurrences (all)	229	0	
Sinus congestion			
subjects affected / exposed	62 / 506 (12.25%)	0 / 11 (0.00%)	
occurrences (all)	102	0	
Rhinorrhoea			
subjects affected / exposed	76 / 506 (15.02%)	0 / 11 (0.00%)	
occurrences (all)	108	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	40 / 506 (7.91%)	0 / 11 (0.00%)	
occurrences (all)	46	0	
Insomnia			
subjects affected / exposed	34 / 506 (6.72%)	0 / 11 (0.00%)	
occurrences (all)	39	0	
Anxiety			

subjects affected / exposed	38 / 506 (7.51%)	0 / 11 (0.00%)	
occurrences (all)	48	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	72 / 506 (14.23%)	0 / 11 (0.00%)	
occurrences (all)	91	0	
Aspartate aminotransferase increased			
subjects affected / exposed	68 / 506 (13.44%)	0 / 11 (0.00%)	
occurrences (all)	82	0	
Bacterial test positive			
subjects affected / exposed	50 / 506 (9.88%)	0 / 11 (0.00%)	
occurrences (all)	82	0	
Blood bilirubin increased			
subjects affected / exposed	31 / 506 (6.13%)	0 / 11 (0.00%)	
occurrences (all)	48	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	72 / 506 (14.23%)	0 / 11 (0.00%)	
occurrences (all)	101	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	26 / 506 (5.14%)	0 / 11 (0.00%)	
occurrences (all)	37	0	
Pulmonary function test decreased			
subjects affected / exposed	30 / 506 (5.93%)	0 / 11 (0.00%)	
occurrences (all)	35	0	
SARS-CoV-2 test positive			
subjects affected / exposed	45 / 506 (8.89%)	0 / 11 (0.00%)	
occurrences (all)	50	0	
Weight decreased			
subjects affected / exposed	32 / 506 (6.32%)	0 / 11 (0.00%)	
occurrences (all)	32	0	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	21 / 506 (4.15%)	1 / 11 (9.09%)	
occurrences (all)	23	1	

Cardiac disorders			
Palpitations			
subjects affected / exposed	11 / 506 (2.17%)	1 / 11 (9.09%)	
occurrences (all)	12	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	38 / 506 (7.51%)	0 / 11 (0.00%)	
occurrences (all)	49	0	
Headache			
subjects affected / exposed	178 / 506 (35.18%)	0 / 11 (0.00%)	
occurrences (all)	335	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	67 / 506 (13.24%)	0 / 11 (0.00%)	
occurrences (all)	96	0	
Nausea			
subjects affected / exposed	91 / 506 (17.98%)	0 / 11 (0.00%)	
occurrences (all)	141	0	
Diarrhoea			
subjects affected / exposed	89 / 506 (17.59%)	0 / 11 (0.00%)	
occurrences (all)	120	0	
Constipation			
subjects affected / exposed	72 / 506 (14.23%)	0 / 11 (0.00%)	
occurrences (all)	97	0	
Abdominal pain upper			
subjects affected / exposed	49 / 506 (9.68%)	0 / 11 (0.00%)	
occurrences (all)	72	0	
Abdominal pain			
subjects affected / exposed	76 / 506 (15.02%)	0 / 11 (0.00%)	
occurrences (all)	106	0	
Abdominal distension			
subjects affected / exposed	31 / 506 (6.13%)	0 / 11 (0.00%)	
occurrences (all)	42	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	57 / 506 (11.26%)	0 / 11 (0.00%)	
occurrences (all)	78	0	

Acne			
subjects affected / exposed	49 / 506 (9.68%)	0 / 11 (0.00%)	
occurrences (all)	57	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	34 / 506 (6.72%)	0 / 11 (0.00%)	
occurrences (all)	46	0	
Neck pain			
subjects affected / exposed	9 / 506 (1.78%)	1 / 11 (9.09%)	
occurrences (all)	9	1	
Myalgia			
subjects affected / exposed	33 / 506 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	38	0	
Back pain			
subjects affected / exposed	51 / 506 (10.08%)	0 / 11 (0.00%)	
occurrences (all)	60	0	
Arthralgia			
subjects affected / exposed	71 / 506 (14.03%)	0 / 11 (0.00%)	
occurrences (all)	106	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	31 / 506 (6.13%)	0 / 11 (0.00%)	
occurrences (all)	34	0	
Cystitis			
subjects affected / exposed	8 / 506 (1.58%)	1 / 11 (9.09%)	
occurrences (all)	13	1	
COVID-19			
subjects affected / exposed	168 / 506 (33.20%)	0 / 11 (0.00%)	
occurrences (all)	208	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	27 / 506 (5.34%)	0 / 11 (0.00%)	
occurrences (all)	37	0	
Viral upper respiratory tract infection			
subjects affected / exposed	36 / 506 (7.11%)	0 / 11 (0.00%)	
occurrences (all)	52	0	
Urinary tract infection			

subjects affected / exposed	43 / 506 (8.50%)	0 / 11 (0.00%)	
occurrences (all)	53	0	
Upper respiratory tract infection			
subjects affected / exposed	120 / 506 (23.72%)	1 / 11 (9.09%)	
occurrences (all)	223	1	
Sinusitis			
subjects affected / exposed	76 / 506 (15.02%)	1 / 11 (9.09%)	
occurrences (all)	126	1	
Rhinitis			
subjects affected / exposed	50 / 506 (9.88%)	0 / 11 (0.00%)	
occurrences (all)	110	0	
Pharyngitis			
subjects affected / exposed	37 / 506 (7.31%)	0 / 11 (0.00%)	
occurrences (all)	54	0	
Nasopharyngitis			
subjects affected / exposed	154 / 506 (30.43%)	0 / 11 (0.00%)	
occurrences (all)	335	0	
Lower respiratory tract infection			
subjects affected / exposed	7 / 506 (1.38%)	1 / 11 (9.09%)	
occurrences (all)	7	1	
Influenza			
subjects affected / exposed	63 / 506 (12.45%)	0 / 11 (0.00%)	
occurrences (all)	72	0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	224 / 506 (44.27%)	3 / 11 (27.27%)	
occurrences (all)	548	3	
Hordeolum			
subjects affected / exposed	18 / 506 (3.56%)	1 / 11 (9.09%)	
occurrences (all)	23	1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	33 / 506 (6.52%)	0 / 11 (0.00%)	
occurrences (all)	42	0	
Decreased appetite			

subjects affected / exposed occurrences (all)	26 / 506 (5.14%) 29	0 / 11 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2018	Updated the study drug regimen to include ivacaftor in place of VX-561 (deuterated ivacaftor), added the number of tablets subjects will receive and tablet strength, and updated guidance on missed doses to account for every 12 hours (q12h) dosing of ivacaftor; Updated statistical analysis plan section for clarity.
19 July 2018	Updated study drug interruption and stopping rules (removed exclusion criteria of isolated total bilirubin elevations).
09 August 2018	Added guidance on concomitant dosing of VX-445/TEZ/IVA with P-glycoprotein (gp) and CYP2C9 substrates based on medicines and healthcare products regulatory agency (MHRA) request.
08 November 2018	Clarified analysis plan for baseline definition and number of pulmonary exacerbations.
17 December 2019	Removed organic anion transporting polypeptides (OATP) 1B1 substrates from prohibited medications list; Added guidance on concomitant dosing of VX-445/TEZ/IVA with OATP1B1, OATP1B3, P-gp, and CYP2C9 substrates; Removed rate of change in percent predicted forced expiratory volume in 1 second (ppFEV1) from Additional Endpoints.
23 June 2020	Extended the Treatment Period to evaluate the long-term efficacy of VX-445/TEZ/IVA beyond 96 weeks of treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported