Clinical trial results:
A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-F508del ELX/TEZ/IVA-responsive CFTR Mutation

Summary

EudraCT number	2021-005320-38
Trial protocol	ES DE FR BE AT IT PT NL SE CZ NO HU PL
Global end of trial date	05 July 2023

Results information

Result version number	v2 (current)
This version publication date	18 August 2024
First version publication date	18 January 2024
Version creation reason	• New data added to full data set Secondary end points information to be updated.

Trial information

Trial identification

Sponsor protocol code	VX21-445-124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05274269
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	25 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2023
Global end of trial reached?	Yes
Global end of trial date	05 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and pharmacodynamics (PD) 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 May 2022
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	Canada: 24
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 81
Worldwide total number of subjects	307
EEA total number of subjects	279

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)	32
Adolescents (12-17 years)	32
Adults (18-64 years)	237
From 65 to 84 years	5
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in CF subjects aged 6 years and older with a non-F508del ELX/TEZ/IVA-responsive cystic fibrosis transmembrane conductance regulator gene (CFTR) mutation.

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	Placebo

Arm description:

Subjects received placebo matched to ELX/TEZ/IVA FDC in the morning and placebo matched to IVA in the evening for 24 weeks.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

Arm title	ELX/TEZ/IVA

Arm description:

Subjects 6 to less than (<) 12 years of age and weighing <30 kilogram (kg) at Day 1 received ELX 100 milligram (mg)/TEZ 50 mg /IVA 75 mg as fixed dose combination (FDC) tablets in the morning and IVA as mono tablet in the evening and those weighing more than or equal to (≥) 30 kg at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 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 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.

Number of subjects in period 1	Placebo	ELX/TEZ/IVA
Started	102	205
Completed	102	197
Not completed	0	8
Adverse Event	-	3
Death	-	1
Other	-	2
Withdrawal of consent (not due to AE)	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to ELX/TEZ/IVA FDC in the morning and placebo matched to IVA in the evening for 24 weeks.

Reporting group title	ELX/TEZ/IVA

Reporting group description:

Subjects 6 to less than (<) 12 years of age and weighing <30 kilogram (kg) at Day 1 received ELX 100 milligram (mg)/TEZ 50 mg /IVA 75 mg as fixed dose combination (FDC) tablets in the morning and IVA as mono tablet in the evening and those weighing more than or equal to (≥) 30 kg at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks.

Reporting group values	Placebo	ELX/TEZ/IVA	Total
Number of subjects	102	205	307
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.9	33.3	
standard deviation	± 16.4	± 15.9	-
Gender categorical Units: Subjects			
Female	52	113	165
Male	50	92	142
Ethnicity Units: Subjects			
Hispanic or Latino	3	8	11
Not Hispanic or Latino	88	171	259
Not Collected per Local Regulations	11	26	37
Race Units: Subjects			
White	86	172	258
Asian	2	4	6
Other	1	3	4
Not Collected per Local Regulations	12	26	38
White, Asian	1	0	1
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: percent predicted FEV1			
arithmetic mean	68.1	67.5	
standard deviation	± 18.1	± 17.6	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to ELX/TEZ/IVA FDC in the morning and placebo matched to IVA in the evening for 24 weeks.

Reporting group title	ELX/TEZ/IVA

Reporting group description:

Subjects 6 to less than (<) 12 years of age and weighing <30 kilogram (kg) at Day 1 received ELX 100 milligram (mg)/TEZ 50 mg /IVA 75 mg as fixed dose combination (FDC) tablets in the morning and IVA as mono tablet in the evening and those weighing more than or equal to (≥) 30 kg at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks.

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

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. The Full Analysis Set (FAS) included all randomized subjects who carry the intended mutation and received at least 1 dose of study drug. 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	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	205		
Units: percent predicted FEV1				
least squares mean (confidence interval 95%)	-0.4 (-2.0 to 1.3)	8.9 (7.7 to 10.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ELX/TEZ/IVA

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Models for Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.2
upper limit	11.3

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. 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	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	200		
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	0.5 (-2.6 to 3.6)	-27.8 (-30.0 to -25.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ELX/TEZ/IVA
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Models for Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	-28.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.1
upper limit	-24.5

Secondary: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain (RD) Score

End point title	Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain (RD) Score

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. FAS. 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	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	202		
Units: units on a scale				
least squares mean (confidence interval 95%)	-2.0 (-5.2 to 1.3)	17.5 (15.2 to 19.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ELX/TEZ/IVA
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	19.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.5
upper limit	23.5

Secondary: Absolute Change in Body Mass Index (BMI)

End point title	Absolute Change in Body Mass Index (BMI)

End point description:

BMI was defined as weight in kilogram (kg) divided by height in square meter (m^2). FAS. 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 at Week 24

End point values	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	196		
Units: kg/m^2				
least squares mean (confidence interval 95%)	0.35 (0.16 to 0.53)	0.81 (0.68 to 0.94)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ELX/TEZ/IVA
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Models for Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.69

Secondary: Absolute Change in Weight

End point title	Absolute Change in Weight

End point description:

FAS. 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 at Week 24

End point values	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	196		
Units: kilogram (kg)				
least squares mean (confidence interval 95%)	1.2 (0.6 to 1.7)	2.4 (2.1 to 2.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ELX/TEZ/IVA
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Model for Repeated Measures
Parameter estimate	LS Mean difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.9

Secondary: Number of Pulmonary Exacerbations (PEx)

End point title	Number of Pulmonary Exacerbations (PEx)

End point description:

Pulmonary exacerbation was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. FAS. 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	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	205		
Units: PEx events				
number (not applicable)	40	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Safety Set was defined as all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 up to Week 28

End point values	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	205		
Units: Subjects				
Subjects with TEAEs	97	193		
Subjects with SAEs	15	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 28	
Adverse event reporting additional description:	
Safety Set was defined as all subjects who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to ELX/TEZ/IVA FDC in the morning and placebo matched to IVA in the evening for 24 weeks.	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Subjects 6 to <12 years of age and weighing <30 kg at Day 1 received ELX 100mg/TEZ 50 mg /IVA 75 mg as FDC tablets in the morning and IVA as mono tablet in the evening and those weighing ≥30 kg at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks. Subjects ≥12 years age at Day 1 received ELX 200 mg/TEZ 100 mg/IVA 150 mg as FDC tablets in the morning and IVA as mono tablet in the evening for 24 weeks.	

Serious adverse events	Placebo	ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 102 (14.71%)	18 / 205 (8.78%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events		0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	1 / 102 (0.98%)	0 / 205 (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			
Drug intolerance			

subjects affected / exposed	1 / 102 (0.98%)	0 / 205 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			

subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic stress disorder			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 102 (0.98%)	0 / 205 (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			
Polyarthritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 102 (0.00%)	2 / 205 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	13 / 102 (12.75%)	5 / 205 (2.44%)	
occurrences causally related to treatment / all	0 / 19	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 102 (0.00%)	1 / 205 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 102 (84.31%)	164 / 205 (80.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 102 (12.75%)	37 / 205 (18.05%)	
occurrences (all)	23	58	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 102 (13.73%)	27 / 205 (13.17%)	
occurrences (all)	17	34	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	13 / 102 (12.75%)	17 / 205 (8.29%)	
occurrences (all)	16	21	
Abdominal pain upper			
subjects affected / exposed	7 / 102 (6.86%)	10 / 205 (4.88%)	
occurrences (all)	8	11	
Constipation			
subjects affected / exposed	4 / 102 (3.92%)	15 / 205 (7.32%)	
occurrences (all)	4	22	
Diarrhoea			
subjects affected / exposed	10 / 102 (9.80%)	26 / 205 (12.68%)	
occurrences (all)	16	49	
Vomiting			
subjects affected / exposed	7 / 102 (6.86%)	15 / 205 (7.32%)	
occurrences (all)	10	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 102 (25.49%)	36 / 205 (17.56%)	
occurrences (all)	39	46	
Haemoptysis			
subjects affected / exposed	6 / 102 (5.88%)	12 / 205 (5.85%)	
occurrences (all)	8	16	
Nasal congestion			
subjects affected / exposed	8 / 102 (7.84%)	6 / 205 (2.93%)	
occurrences (all)	8	6	
Oropharyngeal pain			
subjects affected / exposed	10 / 102 (9.80%)	17 / 205 (8.29%)	
occurrences (all)	11	18	
Productive cough			
subjects affected / exposed	6 / 102 (5.88%)	6 / 205 (2.93%)	
occurrences (all)	6	6	
Sputum increased			
subjects affected / exposed	13 / 102 (12.75%)	20 / 205 (9.76%)	
occurrences (all)	20	25	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 102 (0.98%)	45 / 205 (21.95%)	
occurrences (all)	1	51	
Infections and infestations			
COVID-19			
subjects affected / exposed	10 / 102 (9.80%)	19 / 205 (9.27%)	
occurrences (all)	10	19	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	36 / 102 (35.29%)	28 / 205 (13.66%)	
occurrences (all)	52	36	
Influenza			
subjects affected / exposed	2 / 102 (1.96%)	18 / 205 (8.78%)	
occurrences (all)	2	20	
Nasopharyngitis			
subjects affected / exposed	20 / 102 (19.61%)	42 / 205 (20.49%)	
occurrences (all)	30	58	
Rhinitis			
subjects affected / exposed	6 / 102 (5.88%)	20 / 205 (9.76%)	
occurrences (all)	8	22	
Upper respiratory tract infection			
subjects affected / exposed	10 / 102 (9.80%)	17 / 205 (8.29%)	
occurrences (all)	12	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2022	Amended to add ELX/TEZ/IVA-responsive mutations to the list of qualifying CFTR mutations and adjust for the increased number of qualifying CFTR mutations, the maximum number of subjects with a given CFTR mutation that can be enrolled was decreased.
21 April 2022	Amended to maximum qualifying ppFEV1 value was expanded from 90% to 100%, specified that up to 10% of subjects may be enrolled with a screening ppFEV1 value >90% and ≤100% (approximately 27 subjects) and including history of hypersensitivity exclusion criterion and appendix to specify blood volumes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported