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	v1
This version publication date	18 January 2024
First version publication date	18 January 2024

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	ELX/TEZ/IVA

Arm description:

Subjects 6 to less than (<) 12 year 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.

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.

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

Baseline characteristics

Reporting groups	
Reporting group title	ELX/TEZ/IVA

Reporting group description:

Subjects 6 to less than (<) 12 year 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 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 values	ELX/TEZ/IVA	Placebo	Total
Number of subjects	205	102	307
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.3	33.9	
standard deviation	± 15.9	± 16.4	-
Gender categorical Units: Subjects			
Female	113	52	165
Male	92	50	142

End points

End points reporting groups

Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Subjects 6 to less than (<) 12 year 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 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.	

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:	
End point type	Primary
End point timeframe:	
From Baseline through Week 24	

End point values	ELX/TEZ/IVA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	98		
Units: percentage points				
least squares mean (confidence interval 95%)	8.9 (7.7 to 10.0)	-0.4 (-2.0 to 1.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v ELX/TEZ/IVA
Number of subjects included in analysis	290
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

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Subjects 6 to <12 year 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.	
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.	

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

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

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

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

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

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

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

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

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