Clinical trial results:
A Phase 3b, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 6 Through 11 Years of Age Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

Summary

EudraCT number	2019-003554-86
Trial protocol	DE DK GB FR NL
Global end of trial date	17 May 2021

Results information

Result version number	v2 (current)
This version publication date	14 August 2022
First version publication date	29 November 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	VX19-445-116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04353817
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	14 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2021
Global end of trial reached?	Yes
Global end of trial date	17 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in subjects 6 through 11 years of age with cystic fibrosis (CF), heterozygous for F508del and a minimal function (MF) mutation (F/MF).

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2020
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	Australia: 11
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	United Kingdom: 17
Worldwide total number of subjects	121
EEA total number of subjects	63

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)	121
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in CF subjects 6 through 11 years of age.

Period 1

Period 1 title	Triple Combination Treatment 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 and placebo matched to IVA in the treatment period 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 weighing less than (<) 30 kilograms (kg) at screening received ELX 100 mg once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h) and subjects weighing greater than equals to (>=) 30 kg at screening received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.

Arm type	Experimental
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.

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 fixed-dose combination once daily in the morning.

Number of subjects in period 1	Placebo	ELX/TEZ/IVA
Started	61	60
Completed	61	59
Not completed	0	1
Adverse Event	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to ELX/TEZ/IVA and placebo matched to IVA in the treatment period for 24 weeks.	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Subjects weighing less than (<) 30 kilograms (kg) at screening received ELX 100 mg once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h) and subjects weighing greater than equals to (>=) 30 kg at screening received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.	

Reporting group values	Placebo	ELX/TEZ/IVA	Total
Number of subjects	61	60	121
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.2	9.1	
standard deviation	± 1.7	± 1.8	-
Gender categorical Units: Subjects			
Female	35	35	70
Male	26	25	51
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	42	48	90
Unknown or Not Reported	19	11	30
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	42	45	87
More than one race	0	1	1
Unknown or Not Reported	19	11	30
Lung Clearance Index2.5 (LCI2.5)			
The LCI2.5 index is the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting values and is calculated by dividing the sum of exhaled tidal breaths (cumulative exhaled volume (CEV)) by simultaneously measured functional residual capacity (FRC). An LCI of 7.5 and below is normal; values greater than 7.5 are abnormal. LCI is able to detect abnormalities in lung function earlier than more traditional modalities such as spirometry.			
Units: index			
arithmetic mean	9.75	10.26	
standard deviation	± 1.95	± 2.22	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to ELX/TEZ/IVA and placebo matched to IVA in the treatment period for 24 weeks.	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Subjects weighing less than (<) 30 kilograms (kg) at screening received ELX 100 mg once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h) and subjects weighing greater than equals to (>=) 30 kg at screening received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.	

Primary: Absolute Change in Lung Clearance Index (LCI) 2.5

End point title	Absolute Change in Lung Clearance Index (LCI) 2.5
End point description:	
The LCI2.5 index is the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting values and is calculated by dividing the sum of exhaled tidal breaths (cumulative exhaled volume (CEV)) by simultaneously measured functional residual capacity (FRC). An LCI of 7.5 and below is normal; values greater than 7.5 are abnormal. LCI is able to detect abnormalities in lung function earlier than more traditional modalities such as spirometry. Full analysis set (FAS) included all randomized subjects who carry the intended CFTR allele mutation and receive at least 1 dose of study drug.	
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	61	60		
Units: index				
least squares mean (standard error)	-0.02 (± 0.16)	-2.29 (± 0.16)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	ELX/TEZ/IVA v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-2.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	-1.81

Secondary: Absolute Change in Sweat Chloride (SwCl)

End point title	Absolute Change in Sweat Chloride (SwCl)

End point description:

Sweat samples were collected using an approved collection device. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 24

End point values	Placebo	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	-0.9 (± 1.5)	-52.1 (± 1.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	ELX/TEZ/IVA v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	LS Mean Difference
Point estimate	-51.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.3
upper limit	-47.1

Notes:

[1] - This is the nominal p-value without multiplicity controlled.

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

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

End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

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	61	60		
Units: subjects				
Subjects With TEAEs	57	48		
Subjects With SAEs	9	4		

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	ELX/TEZ/IVA

Reporting group description:

Subjects weighing <30 kg at screening received ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and subjects weighing >=30 kg at screening received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to ELX/TEZ/IVA and placebo matched to IVA in the treatment period for 24 weeks.

Serious adverse events	ELX/TEZ/IVA	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 60 (6.67%)	9 / 61 (14.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Bacterial test positive			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (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			
Phimosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (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			
Lymphadenitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
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			
General physical health deterioration			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal polyps			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
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			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (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	0 / 60 (0.00%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			

subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
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	ELX/TEZ/IVA	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 60 (76.67%)	53 / 61 (86.89%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	
occurrences (all)	3	2	
Alanine aminotransferase increased			
subjects affected / exposed	5 / 60 (8.33%)	3 / 61 (4.92%)	
occurrences (all)	9	4	
Bacterial test positive			
subjects affected / exposed	0 / 60 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
Forced expiratory volume decreased			
subjects affected / exposed	0 / 60 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
Staphylococcus test positive			
subjects affected / exposed	4 / 60 (6.67%)	1 / 61 (1.64%)	
occurrences (all)	4	1	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 60 (30.00%)	12 / 61 (19.67%)	
occurrences (all)	22	20	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 60 (0.00%)	5 / 61 (8.20%)	
occurrences (all)	0	5	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	5 / 60 (8.33%)	17 / 61 (27.87%)	
occurrences (all)	9	27	
Diarrhoea			
subjects affected / exposed	4 / 60 (6.67%)	6 / 61 (9.84%)	
occurrences (all)	4	6	
Abdominal pain upper			
subjects affected / exposed	4 / 60 (6.67%)	5 / 61 (8.20%)	
occurrences (all)	4	7	
Steatorrhoea			
subjects affected / exposed	3 / 60 (5.00%)	0 / 61 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	1 / 60 (1.67%)	5 / 61 (8.20%)	
occurrences (all)	1	6	
Vomiting			
subjects affected / exposed	3 / 60 (5.00%)	4 / 61 (6.56%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 60 (23.33%)	26 / 61 (42.62%)	
occurrences (all)	17	40	
Nasal polyps			
subjects affected / exposed	0 / 60 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	5	
Nasal congestion			
subjects affected / exposed	3 / 60 (5.00%)	3 / 61 (4.92%)	
occurrences (all)	3	4	
Productive cough			
subjects affected / exposed	7 / 60 (11.67%)	6 / 61 (9.84%)	
occurrences (all)	8	7	
Rhinorrhoea			
subjects affected / exposed	7 / 60 (11.67%)	7 / 61 (11.48%)	
occurrences (all)	9	7	
Oropharyngeal pain			

subjects affected / exposed	3 / 60 (5.00%)	12 / 61 (19.67%)	
occurrences (all)	4	14	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 60 (6.67%)	0 / 61 (0.00%)	
occurrences (all)	5	0	
Rash			
subjects affected / exposed	6 / 60 (10.00%)	3 / 61 (4.92%)	
occurrences (all)	6	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 60 (1.67%)	4 / 61 (6.56%)	
occurrences (all)	2	4	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 60 (1.67%)	14 / 61 (22.95%)	
occurrences (all)	1	16	
Nasopharyngitis			
subjects affected / exposed	7 / 60 (11.67%)	9 / 61 (14.75%)	
occurrences (all)	8	12	
Rhinitis			
subjects affected / exposed	3 / 60 (5.00%)	5 / 61 (8.20%)	
occurrences (all)	3	5	
Upper respiratory tract infection			
subjects affected / exposed	3 / 60 (5.00%)	5 / 61 (8.20%)	
occurrences (all)	4	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported