



Clinical trial results:

A Phase 3b Open label Study Evaluating the Long term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Cystic Fibrosis Subjects Ages 6 Years and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

Summary

EudraCT number	2020-001404-42
Trial protocol	GB DE DK NL FR
Global end of trial date	24 March 2023

Results information

Result version number	v2 (current)
This version publication date	25 May 2024
First version publication date	08 October 2023
Version creation reason	New data added to full data set Final result is updated in draft

Trial information

Trial identification

Sponsor protocol code	VX20-445-119
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04545515
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, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 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	20 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 March 2023
Global end of trial reached?	Yes
Global end of trial date	24 March 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 elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in subjects with Cystic Fibrosis (CF)

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	11 January 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	23 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 8
Worldwide total number of subjects	120
EEA total number of subjects	62

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	120
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:

A total of 120 subjects from the parent study VX19-445-116 (NCT04353817) enrolled in this study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ELX/TEZ/IVA
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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 ($\geq$) 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 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects $\geq$ 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 96 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 fixed dose combination (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	ELX/TEZ/IVA
Started	120
Placebo-ELX/TEZ/IVA	61 ^[1]
ELX/TEZ/IVA-ELX/TEZ/IVA	59 ^[2]
Completed	110
Not completed	10

Adverse event	1
Withdrawal of consent (not due to AE)	2
Commercial drug is available for subject	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects from the Placebo group of the parent study VX19-445-116, who received ELX/TEZ/IVA during the current study VX20-445-119.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Subjects from the ELX/TEZ/IVA group of the parent study VX19-445-116, who continued to receive ELX/TEZ/IVA during the current study VX20-445-119.

Baseline characteristics

Reporting groups

Reporting group title	Overall Period
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Reporting group description:

Baseline data for the long-term safety analysis is based on the parent study baseline, which is defined as the most recent non-missing measurement collected before the first dose of study drug in the treatment period of parent study.

Reporting group values	Overall Period	Total	
Number of subjects	120	120	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	9.1 ± 1.7	-	
Gender categorical Units: Subjects			
Female	69	69	
Male	51	51	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	90	90	
Not collected per local regulations	29	29	
Race Units: Subjects			
White	87	87	
Black or African American	1	1	
Asian	1	1	
American Indian or Alaska Native	1	1	
Other	1	1	
Not collected per local Regulations	28	28	
Multiracial	1	1	

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 ($\geq$) 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 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects $\geq$ 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 96 weeks.	

Primary: 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) ^[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 Open label extension (OLE) study.	
End point type	Primary
End point timeframe: From Baseline up to Week 100	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were planned. No statistical comparisons were planned for the primary safety endpoint.

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Subjects				
Subjects With TEAEs	118			
Subjects With SAEs	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Parent Study Baseline in Sweat Chloride (SwCl)

End point title	Absolute Change From Parent Study Baseline in Sweat Chloride (SwCl)
End point description: Sweat samples were collected using an approved collection device. The OL Full Analysis Set (OL-FAS) is defined as all enrolled subjects who have received at least 1 dose of study drug in the open-label extension study. Data were planned to be presented as per parent study reporting groups (i.e., Placebo-ELX/TEZ/IVA and ELX/TEZ/IVA-ELX/TEZ/IVA). Here, "n" signifies subjects who were evaluable in the	

specified parent study reporting group at OL Week 96.

End point type	Secondary
End point timeframe:	
From Parent Study Baseline to Week 96	

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: millimole per liter (mmol/L)				
least squares mean (standard error)				
Placebo-ELX/TEZ/IVA (n=52)	-57.3 (± 2.2)			
ELX/TEZ/IVA-ELX/TEZ/IVA (n=46)	-57.5 (± 2.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Parent Study Baseline in Lung Clearance Index 2.5 (LCI2.5)

End point title	Absolute Change From Parent Study Baseline in Lung Clearance Index 2.5 (LCI2.5)
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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. OL-FAS. Data were planned to be presented as per parent study reporting groups (i.e., Placebo-ELX/TEZ/IVA and ELX/TEZ/IVA-ELX/TEZ/IVA). Here, "n" signifies subjects who were evaluable in the specified parent study reporting group at OL Week 96.

End point type	Secondary
End point timeframe:	
From Parent Study Baseline to Week 96	

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	104			
Units: Index				
least squares mean (standard error)				
Placebo-ELX/TEZ/IVA (n=56)	-1.74 (± 0.18)			
ELX/TEZ/IVA-ELX/TEZ/IVA (n=48)	-2.35 (± 0.19)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 100

Adverse event reporting additional description:

The OL-SS included all subjects who had received at least 1 dose of study drug in the OLE study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	ELX/TEZ/IVA
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Reporting group description:

Subjects 6 to <12 year of age and weighing <30 kg at Day 1 received ELX 100 mg/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 96 weeks. Doses were adjusted upward with subsequent changes in weight. 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 96 weeks.

Serious adverse events	ELX/TEZ/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 120 (10.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Steatorrhoea			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia staphylococcal			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia pseudomonal			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 120 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bacterial disease carrier			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight gain poor			
subjects affected / exposed	1 / 120 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ELX/TEZ/IVA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 120 (98.33%)		
Investigations			
Staphylococcus test positive			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	12		
SARS-CoV-2 test positive			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	13		
Bacterial test positive			

subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 10 6 / 120 (5.00%) 8 11 / 120 (9.17%) 15		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	45 / 120 (37.50%) 106		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	48 / 120 (40.00%) 85 6 / 120 (5.00%) 8		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 13		
Immune system disorders Immunisation reaction subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 12		
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	7 / 120 (5.83%) 12		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting	9 / 120 (7.50%) 13		

subjects affected / exposed	24 / 120 (20.00%)		
occurrences (all)	42		
Abdominal pain			
subjects affected / exposed	27 / 120 (22.50%)		
occurrences (all)	44		
Abdominal pain upper			
subjects affected / exposed	11 / 120 (9.17%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed	8 / 120 (6.67%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	15 / 120 (12.50%)		
occurrences (all)	22		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	62 / 120 (51.67%)		
occurrences (all)	163		
Nasal congestion			
subjects affected / exposed	13 / 120 (10.83%)		
occurrences (all)	15		
Oropharyngeal pain			
subjects affected / exposed	32 / 120 (26.67%)		
occurrences (all)	51		
Productive cough			
subjects affected / exposed	17 / 120 (14.17%)		
occurrences (all)	30		
Rhinorrhoea			
subjects affected / exposed	22 / 120 (18.33%)		
occurrences (all)	50		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	9 / 120 (7.50%)		
occurrences (all)	12		
Infections and infestations			

Bacterial disease carrier subjects affected / exposed occurrences (all)	8 / 120 (6.67%) 11		
COVID-19 subjects affected / exposed occurrences (all)	70 / 120 (58.33%) 78		
Hordeolum subjects affected / exposed occurrences (all)	10 / 120 (8.33%) 12		
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	19 / 120 (15.83%) 27		
Influenza subjects affected / exposed occurrences (all)	11 / 120 (9.17%) 12		
Nasopharyngitis subjects affected / exposed occurrences (all)	54 / 120 (45.00%) 115		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	13 / 120 (10.83%) 17		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	37 / 120 (30.83%) 65		
Rhinitis subjects affected / exposed occurrences (all)	29 / 120 (24.17%) 50		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 120 (5.00%) 9		

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