



## 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	v1
This version publication date	08 October 2023
First version publication date	08 October 2023

#### 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	Safety, Efficacy
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	Netherlands: 7
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 17
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	Australia: 11
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Israel: 5
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:

Subjects from the parent study VX19-445-116 (NCT04353817) were enrolled in this study. A total of 120 subjects were 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) once daily (qd) /TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h) and those weighing more than or equal to ( $\geq$ ) 30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h for 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects  $\geq$ 12 years age at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h 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
Completed	110
Not completed	10
Adverse event	1
Withdrawal of consent (not due to AE)	2

Commercial drug is available for subject	7
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## Baseline characteristics

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### 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.

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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	

## End points

### End points reporting groups

Reporting group title	ELX/TEZ/IVA
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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) once daily (qd) /TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h) and those weighing more than or equal to ( $\geq$ ) 30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h for 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects  $\geq$ 12 years age at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h 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) <sup>[1]</sup>
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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
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End point timeframe:

From Day 1 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

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 100

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 qd /TEZ 50 mg qd/IVA 75 mg q12h and those weighing ≥30 kg at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h for 96 weeks. Doses were adjusted upward with subsequent changes in weight. Subjects ≥12 years age at Day 1 received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h 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		
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		
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		
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		

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		
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		
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			
SARS-CoV-2 test positive			
subjects affected / exposed	12 / 120 (10.00%)		
occurrences (all)	13		
Bacterial test positive			
subjects affected / exposed	7 / 120 (5.83%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 120 (5.00%)		
occurrences (all)	8		
Alanine aminotransferase increased			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Staphylococcus test positive</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 120 (9.17%)</p> <p>15</p> <p>9 / 120 (7.50%)</p> <p>12</p>		
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>45 / 120 (37.50%)</p> <p>106</p>		
<p>General disorders and administration site conditions</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>48 / 120 (40.00%)</p> <p>85</p> <p>6 / 120 (5.00%)</p> <p>8</p>		
<p>Ear and labyrinth disorders</p> <p>Ear pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 120 (6.67%)</p> <p>13</p>		
<p>Immune system disorders</p> <p>Immunisation reaction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 120 (6.67%)</p> <p>12</p>		
<p>Eye disorders</p> <p>Conjunctivitis allergic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 120 (5.83%)</p> <p>12</p>		
<p>Gastrointestinal disorders</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p>	<p>8 / 120 (6.67%)</p> <p>8</p> <p>11 / 120 (9.17%)</p> <p>13</p>		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>27 / 120 (22.50%)</p> <p>44</p> <p>15 / 120 (12.50%)</p> <p>22</p> <p>9 / 120 (7.50%)</p> <p>13</p> <p>24 / 120 (20.00%)</p> <p>42</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Productive cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rhinorrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>17 / 120 (14.17%)</p> <p>30</p> <p>62 / 120 (51.67%)</p> <p>163</p> <p>13 / 120 (10.83%)</p> <p>15</p> <p>32 / 120 (26.67%)</p> <p>51</p> <p>22 / 120 (18.33%)</p> <p>50</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 120 (7.50%)</p> <p>12</p>		
<p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p>	<p>54 / 120 (45.00%)</p> <p>115</p>		

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported