

**Clinical trial results:****A Phase 3b Open-label Study Evaluating the Effects of Elexacaftor/Tezacaftor/Ivacaftor on Cough and Physical Activity in Cystic Fibrosis Subjects 12 Years of Age and Older Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)****Summary**

EudraCT number	2021-001628-16
Trial protocol	ES BE
Global end of trial date	26 July 2022

Results information

Result version number	v1
This version publication date	08 February 2023
First version publication date	08 February 2023

Trial information**Trial identification**

Sponsor protocol code	VX20-445-126
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04969224
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 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2022
Global end of trial reached?	Yes
Global end of trial date	26 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on cough and physical activity using wearable technology in Cystic Fibrosis(CF) subjects.

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	12 October 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Australia: 37
Worldwide total number of subjects	82
EEA total number of subjects	38

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)	0
Adolescents (12-17 years)	24
Adults (18-64 years)	58
From 65 to 84 years	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in subjects with cystic fibrosis, aged 12 years and older, who are heterozygous for the F508del mutation and the minimal function mutation (F/MF).

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 received ELX/TEZ/IVA fixed-dose combination (FDC) in the morning and IVA in the evening.

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 combination 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 dose once daily in the evening.

Number of subjects in period 1 ^[1]	ELX/TEZ/IVA
Started	81
Completed	80
Not completed	1
Adverse event	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 82 subjects were enrolled in the study. One subject was enrolled but not dosed in this study. Therefore, data for 81 subjects are reported in the subject disposition and baseline characteristics sections.

Baseline characteristics

Reporting groups

Reporting group title	Overall Period
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Reporting group description:

Subjects received ELX/TEZ/IVA fixed-dose combination (FDC) in the morning and IVA in the evening.

Reporting group values	Overall Period	Total	
Number of subjects	81	81	
Age categorical Units: Subjects			
Less than (<)18 years	24	24	
More than or equal to (\geq)18 years	57	57	
Age continuous Units: years			
arithmetic mean	25.7		
standard deviation	± 9.6	-	
Gender categorical Units: Subjects			
Female	37	37	
Male	44	44	

End points

End points reporting groups

Reporting group title	ELX/TEZ/IVA
Reporting group description: Subjects received ELX/TEZ/IVA fixed-dose combination (FDC) in the morning and IVA in the evening.	

Primary: Percent Reduction From Baseline in Cough Frequency (cough events per day) to the Average of Week 8 Through Week 12

End point title	Percent Reduction From Baseline in Cough Frequency (cough events per day) to the Average of Week 8 Through Week 12 ^[1]
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End point description:

End point type	Primary
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End point timeframe:

Baseline, Week 8 through Week 12

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: Participants' post-baseline values were compared to their baseline values with a mixed model for repeated measures with change from baseline at each post-baseline visit on the natural log scale as the dependent variable. The primary result obtained from the model was the estimated percent reduction in cough frequency from baseline to the average of Week 8 through Week 12, i.e. $100\% \times (1 - \exp(\text{LS mean}))$.

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percent				
number (confidence interval 95%)	91.7 (89.2 to 93.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 17

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

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

Subjects received ELX/TEZ/IVA FDC in the morning and IVA in the evening.

Serious adverse events	ELX/TEZ/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 81 (2.47%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 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	56 / 81 (69.14%)		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	14 / 81 (17.28%) 19		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 10		
Abdominal pain upper subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 7		
Diarrhoea subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 13		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 6		
Nasal congestion subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5		
Oropharyngeal pain subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 8		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 6		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 81 (16.05%) 15		
COVID-19 subjects affected / exposed occurrences (all)	13 / 81 (16.05%) 15		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 7		

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