



## Clinical trial results:

### A Phase 3b, Randomized, Double blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del

#### Summary

EudraCT number	2019-001735-31
Trial protocol	GB BE
Global end of trial date	24 July 2020

#### Results information

Result version number	v1
This version publication date	06 February 2021
First version publication date	06 February 2021

#### Trial information

##### Trial identification

Sponsor protocol code	VX18-445-109
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04105972
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	11 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2020
Global end of trial reached?	Yes
Global end of trial date	24 July 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-445/TEZ/IVA in CF subjects, homozygous for F508del (F/F).

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	03 October 2019
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	United Kingdom: 88
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Australia: 30
Worldwide total number of subjects	176
EEA total number of subjects	146

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)	53
Adults (18-64 years)	123
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 cystic fibrosis (CF) subjects aged 12 years or older.

### 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
<b>Arm title</b>	TEZ/IVA

Arm description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	TEZ/IVA
Investigational medicinal product code	VX-661/VX-770
Other name	Tezacaftor/Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 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.

<b>Arm title</b>	ELX/TEZ/IVA
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Arm description:

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period 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.

<b>Number of subjects in period 1<sup>[1]</sup></b>	TEZ/IVA	ELX/TEZ/IVA
Started	88	87
Completed	86	86
Not completed	2	1
Adverse Event	2	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 176 subjects enrolled in the study. Out of those 176 subjects, 1 subject was randomized but not dosed in the treatment period. Therefore, only 175 subjects are included in the subject disposition and baseline section.

## Baseline characteristics

### Reporting groups

Reporting group title	TEZ/IVA
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Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.

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

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.

Reporting group values	TEZ/IVA	ELX/TEZ/IVA	Total
Number of subjects	88	87	175
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	27.8 ± 11.0	27.9 ± 11.8	-
Gender categorical Units: Subjects			
Female	45	43	88
Male	43	44	87

## End points

### End points reporting groups

Reporting group title	TEZ/IVA
Reporting group description: Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.	
Reporting group title	ELX/TEZ/IVA
Reporting group description: Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.	

### Primary: Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score

End point title	Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score
End point description:	
End point type	Primary
End point timeframe: From Baseline Through Week 24	

End point values	TEZ/IVA	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	87		
Units: units on scale				
least squares mean (confidence interval 95%)	1.2 (-1.7 to 4.2)	17.1 (14.1 to 20.1)		

### Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	ELX/TEZ/IVA v TEZ/IVA
Number of subjects included in analysis	175
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	15.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	20.1

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 in the treatment period up to 28 days after last dose of study drug or to the completion of study participation date, whichever occurs first (up to Week 28)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	TEZ/IVA
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Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ/IVA in the treatment period for 24 weeks.

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

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.

Serious adverse events	TEZ/IVA	ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 88 (15.91%)	5 / 87 (5.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
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	1 / 88 (1.14%)	0 / 87 (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 / 88 (1.14%)	0 / 87 (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			
subjects affected / exposed	1 / 88 (1.14%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obsessive-compulsive disorder			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (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			
Nephrolithiasis			

subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	9 / 88 (10.23%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Lower respiratory tract infection</b>			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
Type 3 diabetes mellitus			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
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 %

<b>Non-serious adverse events</b>	TEZ/IVA	ELX/TEZ/IVA	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	72 / 88 (81.82%)	59 / 87 (67.82%)	
<b>Investigations</b>			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 88 (1.14%)	6 / 87 (6.90%)	
occurrences (all)	2	7	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 88 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	6	
Bacterial test positive			
subjects affected / exposed	5 / 88 (5.68%)	1 / 87 (1.15%)	
occurrences (all)	8	1	
<b>Nervous system disorders</b>			

Headache subjects affected / exposed occurrences (all)	18 / 88 (20.45%) 26	25 / 87 (28.74%) 38	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	7 / 88 (7.95%) 10	4 / 87 (4.60%) 6	
Diarrhoea subjects affected / exposed occurrences (all)	7 / 88 (7.95%) 8	8 / 87 (9.20%) 10	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	23 / 88 (26.14%) 32	11 / 87 (12.64%) 17	
Haemoptysis subjects affected / exposed occurrences (all)	6 / 88 (6.82%) 8	3 / 87 (3.45%) 3	
Nasal congestion subjects affected / exposed occurrences (all)	0 / 88 (0.00%) 0	6 / 87 (6.90%) 6	
Oropharyngeal pain subjects affected / exposed occurrences (all)	7 / 88 (7.95%) 8	11 / 87 (12.64%) 12	
Productive cough subjects affected / exposed occurrences (all)	3 / 88 (3.41%) 4	8 / 87 (9.20%) 10	
Sputum increased subjects affected / exposed occurrences (all)	16 / 88 (18.18%) 18	10 / 87 (11.49%) 10	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 88 (0.00%) 0	7 / 87 (8.05%) 8	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	32 / 88 (36.36%)	10 / 87 (11.49%)	
occurrences (all)	38	12	
Nasopharyngitis			
subjects affected / exposed	13 / 88 (14.77%)	17 / 87 (19.54%)	
occurrences (all)	18	19	
Upper respiratory tract infection			
subjects affected / exposed	5 / 88 (5.68%)	9 / 87 (10.34%)	
occurrences (all)	6	11	

## 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