

**Clinical trial results:****A Phase 3b Open-label Study to Assess the Effect of Elexacaftor/Tezacaftor/Ivacaftor on Glucose Tolerance in Cystic Fibrosis Subjects with Abnormal Glucose Metabolism****Summary**

EudraCT number	2020-003170-44
Trial protocol	BE CZ FR NL IT
Global end of trial date	14 July 2022

Results information

Result version number	v1
This version publication date	29 January 2023
First version publication date	29 January 2023

Trial information**Trial identification**

Sponsor protocol code	VX19-445-117
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04599465
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	19 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2022
Global end of trial reached?	Yes
Global end of trial date	14 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) on glucose tolerance in Cystic Fibrosis (CF) subjects with impaired glucose tolerance (IGT) or CF-related diabetes (CFRD)

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	15 January 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	Australia: 11
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	69
EEA total number of subjects	58

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)	19

Adults (18-64 years)	50
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 subjects with CF aged 12 years and older who are heterozygous for the F508del mutation and a minimal function mutation (F/MF genotypes), with abnormal glucose metabolism.

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 ivacaftor (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	ELX/TEZ/IVA
Started	69
Completed	66
Not completed	3
Physician decision	1
Withdrawal of consent (not due to AE)	2

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 ivacaftor (IVA) in the evening.

Reporting group values	Overall Period	Total	
Number of subjects	69	69	
Age categorical Units: Subjects			
Less than (<)18 years	19	19	
More than or equal to (\geq)18 years	50	50	
Age continuous Units: years			
arithmetic mean	25.1		
standard deviation	± 9.5	-	
Gender categorical Units: Subjects			
Female	31	31	
Male	38	38	

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 ivacaftor (IVA) in the evening.	

Primary: Change From Baseline in 2-hour Blood Glucose Levels Following an Oral Glucose Tolerance Test (OGTT) to the Average of Week 36 and Week 48

End point title	Change From Baseline in 2-hour Blood Glucose Levels Following an Oral Glucose Tolerance Test (OGTT) to the Average of Week 36 and Week 48 ^[1]
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End point description:

End point type	Primary
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End point timeframe:

Baseline, Week 36 and 48

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: This is a single arm study, and thus no between-group comparisons were planned. However, participants' post-baseline values were compared to their pre-treatment baseline values with a mixed model for repeated measures (MMRM) with change from baseline in 2-hour post-OGTT blood glucose levels at each post-baseline visit as the dependent variable. The primary result obtained from the model was the estimated mean change from baseline to the average of Week 36 and Week 48.

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: milligrams per deciliter (mg/dl)				
least squares mean (confidence interval 95%)	-35.0 (-49.2 to -20.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 52

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 fixed dose combination (FDC) in the morning and ivacaftor (IVA) in the evening.

Serious adverse events	ELX/TEZ/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 69 (8.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Heavy menstrual bleeding			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 69 (1.45%)		
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	62 / 69 (89.86%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	5		
Alanine aminotransferase increased			

<p>subjects affected / exposed occurrences (all)</p> <p>Blood bilirubin increased subjects affected / exposed occurrences (all)</p> <p>Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)</p>	<p>6 / 69 (8.70%) 6</p> <p>7 / 69 (10.14%) 7</p> <p>5 / 69 (7.25%) 6</p>		
<p>Nervous system disorders Headache subjects affected / exposed occurrences (all)</p>	<p>16 / 69 (23.19%) 22</p>		
<p>General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)</p> <p>Pyrexia subjects affected / exposed occurrences (all)</p>	<p>5 / 69 (7.25%) 5</p> <p>16 / 69 (23.19%) 22</p>		
<p>Immune system disorders Immunisation reaction subjects affected / exposed occurrences (all)</p>	<p>6 / 69 (8.70%) 9</p>		
<p>Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)</p> <p>Diarrhoea subjects affected / exposed occurrences (all)</p> <p>Abdominal pain upper subjects affected / exposed occurrences (all)</p> <p>Nausea subjects affected / exposed occurrences (all)</p>	<p>9 / 69 (13.04%) 13</p> <p>13 / 69 (18.84%) 16</p> <p>8 / 69 (11.59%) 9</p> <p>6 / 69 (8.70%) 6</p>		

Vomiting subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 9		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	11 / 69 (15.94%) 12		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Oropharyngeal pain subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 9		
Productive cough subjects affected / exposed occurrences (all)	5 / 69 (7.25%) 7		
Sputum increased subjects affected / exposed occurrences (all)	12 / 69 (17.39%) 13		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Rash subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 10		
Infections and infestations			
COVID-19 subjects affected / exposed occurrences (all)	22 / 69 (31.88%) 22		
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	10 / 69 (14.49%) 14		
Influenza subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 6		

Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 69 (21.74%) 17		
Rhinitis subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 11		
Tonsillitis subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 4		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5		
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2020	Removed option for use of remote measures at certain study visits such that those visits are to be performed in the clinic; clarified different glomerular filtration rates for subjects ≥ 18 years of age and subjects < 18 years of age; clarified that during in-clinic visits, spirometry assessments may be performed on more than 1 spirometer, as applicable; removed sweat chloride assessment at Week 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported