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	v2 (current)
This version publication date	20 August 2023
First version publication date	29 January 2023
Version creation reason	• New data added to full data set Addition of Secondary data

Trial information

Trial identification

Sponsor protocol code	VX19-445-117

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	France: 13
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Belgium: 7
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

Arm description:

Subjects received elexacaftor (ELX) 200 milligram (mg)/ tezacaftor (TEZ) 100 mg/ ivacaftor (IVA)150 mg in the morning and IVA 150 mg 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
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 (≥)18 years	50	50	
Gender categorical Units: Subjects			
Female	31	31	
Male	38	38	
Ethnicity Units: Subjects			
Hispanic or Latino	8	8	
Not Hispanic or Latino	41	41	
Not collected per local regulations	20	20	
Race Units: Subjects			
White	48	48	
Black or African American	0	0	
Asian	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Other	1	1	
Not collected per local regulations	20	20	
2-hour Post-OGTT Blood Glucose Levels			
Baseline 2-hour post-Oral Glucose Tolerance Test (OGTT) blood glucose level was defined as the average of valid pre-dose measurements at screening and Day 1. OGTT results were considered valid only when the subjects was fasting for at least 8 hours.			
Units: milligrams per deciliter (mg/dl)			
arithmetic mean	217.6		
standard deviation	± 73.1	-	

End points

End points reporting groups

Reporting group title	ELX/TEZ/IVA

Reporting group description:

Subjects received elexacaftor (ELX) 200 milligram (mg)/ tezacaftor (TEZ) 100 mg/ ivacaftor (IVA)150 mg in the morning and IVA 150 mg in the evening.

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

End point title	Change From Baseline in 2-hour Blood Glucose Levels Following an OGTT to the Average of Week 36 and Week 48[1]

End point description:

Baseline 2-hour post-OGTT blood glucose level was defined as the average of valid pre-dose measurements at screening and Day 1. OGTT results were considered valid only when the subject was fasting for at least 8 hours. The Full Analysis Set (FAS) will include all enrolled subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug.

End point type	Primary

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, subjects' 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

Secondary: Percentage of Subjects With Improvement in Dysglycemia Categorization at Week 48

End point title	Percentage of Subjects With Improvement in Dysglycemia Categorization at Week 48

End point description:

Baseline dysglycemia category was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period. Improvement in dysglycemia is to change from cystic fibrosis-related diabetes (CFRD) at baseline to impaired glucose tolerance (IGT)/normal glucose tolerance (NGT) at Week 48 OR change from IGT at baseline to NGT at Week 48. CFRD: 2-hour post-OGTT blood glucose level ≥200 mg/dL or fasting blood glucose level ≥126 mg/dL; IGT: 2-hour post-

OGTT blood glucose level ≥140 to <200 mg/dL and fasting blood glucose level <126 mg/dL; NGT: 2 hour post-OGTT blood glucose level <140 mg/dL and fasting blood glucose level <126 mg/dL. FAS subjects with abnormal glucose tolerance at baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: percentage of subjects				
number (confidence interval 95%)	37.7 (24.8 to 52.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: 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)

End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

End point type	Secondary

End point timeframe:

Day 1 up to Week 52

End point values	ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: Subjects				
Subjects with TEAEs	67			
Subjects with SAEs	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 52	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX 200 mg/ TEZ 100 mg/ IVA 150 mg in the morning and IVA 150 mg 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			

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

Vomiting subjects affected / exposed occurrences (all)	7 / 69 (10.14%) 9		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Sputum increased subjects affected / exposed occurrences (all)	 11 / 69 (15.94%) 12 5 / 69 (7.25%) 7 8 / 69 (11.59%) 9 4 / 69 (5.80%) 4 12 / 69 (17.39%) 13		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Acne subjects affected / exposed occurrences (all)	 7 / 69 (10.14%) 10 4 / 69 (5.80%) 4		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 22 / 69 (31.88%) 22 6 / 69 (8.70%) 6 15 / 69 (21.74%) 17		

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	14		
Tonsillitis			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	11		
Upper respiratory tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	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.
26 April 2021	Updated the definition of IGT to 2 hour post-OGTT blood glucose level ≥140 to <200 mg/dL (≥7.77 to <11.10 mmol/L) to eliminate a gap in glucose values in previous protocol versions, and to clarify both the glucose values (in mmol/L) and the dysglycemia categories; Updated the definition of CFRD to either fasting hyperglycemia (blood glucose level ≥126 mg/dL [≥7.00 mmol/L] after an 8 hour fast) or 2 hour post OGTT blood glucose level ≥200 mg/dL (≥11.10 mmol/L) to eliminate a gap in glucose values in previous protocol versions, and to clarify both the glucose values (in mmol/L) and the dysglycemia categories; Added a waiver of the Safety Follow-up Visit for subjects who complete the Week 48 Visit and transition to a commercially available CFTR modulator regimen within 28 days after the last dose of study drug, given the possibility of commercial availability of ELX/TEZ/IVA in certain countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported