Clinical trial results:
A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

Summary

EudraCT number	2018-002835-76
Trial protocol	GB IE DE DK FR BE NL IT
Global end of trial date	12 June 2020

Results information

Result version number	v1
This version publication date	26 December 2020
First version publication date	26 December 2020

Trial information

Trial identification

Sponsor protocol code	VX18-445-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04058353
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	30 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2020
Global end of trial reached?	Yes
Global end of trial date	12 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in cystic fibrosis (CF) subjects who are heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes).

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	28 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 92
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Denmark: 2
Worldwide total number of subjects	271
EEA total number of subjects	140

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)	242
From 65 to 84 years	5
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
Arm title	Control: IVA or TEZ/IVA

Arm description:

Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA or TEZ/IVA in the treatment period for 8 weeks.

Arm type	Active comparator
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 every 12 hours.

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 once daily and IVA every 12 hours.

Arm title	Triple Combination (TC): ELX/TEZ/IVA

Arm description:

Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA TC in the treatment period for 8 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 VX-445/TEZ/IVA fixed dose 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 once daily in the evening.

Number of subjects in period 1[1]	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA
Started	126	132
Completed	122	131
Not completed	4	1
Physician decision	1	-
Other	1	-
Adverse Events	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 271 subjects enrolled, 12 subjects discontinued in run-in period of the study. Of 259 subjects, 1 subject randomized but not dosed in the treatment period. Therefore, only 258 subjects are included in the subject disposition and baseline section.

Baseline characteristics

Reporting groups	
Reporting group title	Control: IVA or TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA or TEZ/IVA in the treatment period for 8 weeks.	
Reporting group title	Triple Combination (TC): ELX/TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA TC in the treatment period for 8 weeks.	

Reporting group values	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA	Total
Number of subjects	126	132	258
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	37.6	37.7	
standard deviation	± 14.3	± 14.7	-
Gender categorical			
Units: Subjects			
Female	61	67	128
Male	65	65	130

End points

End points reporting groups

Reporting group title	Control: IVA or TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA or TEZ/IVA in the treatment period for 8 weeks.	
Reporting group title	Triple Combination (TC): ELX/TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA TC in the treatment period for 8 weeks.	

Primary: Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) for the ELX/TEZ/IVA group

End point title	Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) for the ELX/TEZ/IVA group[1][2]
End point description:	
End point type	Primary
End point timeframe:	
From Baseline Through Week 8	

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 within treatment group comparison was planned for this endpoint. Individual within-group comparison cannot be reported in the EudraCT database. Therefore, no statistical comparisons are reported.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is applicable only for the triple combination arm.

End point values	Triple Combination (TC): ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: percentage points				
least squares mean (confidence interval 95%)	3.7 (2.8 to 4.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Control: IVA or TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA or TEZ/IVA in the treatment period for 8 weeks.	
Reporting group title	Triple Combination (TC): ELX/TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects received ELX/TEZ/IVA TC in the treatment period for 8 weeks.	

Serious adverse events	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 126 (8.73%)	5 / 132 (3.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 126 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	7 / 126 (5.56%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 126 (37.30%)	35 / 132 (26.52%)	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 126 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	9	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 126 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	8	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 126 (15.08%)	11 / 132 (8.33%)	
occurrences (all)	30	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 126 (1.59%)	7 / 132 (5.30%)	
occurrences (all)	2	7	
Diarrhoea			
subjects affected / exposed	8 / 126 (6.35%)	5 / 132 (3.79%)	
occurrences (all)	13	5	
Nausea			
subjects affected / exposed	9 / 126 (7.14%)	2 / 132 (1.52%)	
occurrences (all)	16	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 126 (14.29%)	3 / 132 (2.27%)	
occurrences (all)	21	3	
Sputum increased			
subjects affected / exposed	8 / 126 (6.35%)	6 / 132 (4.55%)	
occurrences (all)	8	6	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	10 / 126 (7.94%)	2 / 132 (1.52%)	
occurrences (all)	11	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2019	Amended to add an exploratory endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported