



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 Minimal Function Mutation (F/MF)

Summary

EudraCT number	2018-000183-28
Trial protocol	SE DE GB CZ BE NL AT GR FR IT
Global end of trial date	24 April 2019

Results information

Result version number	v1
This version publication date	20 November 2019
First version publication date	20 November 2019

Trial information

Trial identification

Sponsor protocol code	VX17-445-102
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03525444
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)	Yes
EMA paediatric investigation plan number(s)	EMA-002324-PIP01-17
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 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2019
Global end of trial reached?	Yes
Global end of trial date	24 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are heterozygous for the F508del and a minimal function mutation (F/MF subjects).

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	15 June 2018
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	Canada: 24
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	United States: 216
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Greece: 3
Worldwide total number of subjects	405
EEA total number of subjects	141

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)	116
Adults (18-64 years)	289
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 cystic fibrosis (CF) 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	Placebo
------------------	---------

Arm description:

Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-445/TEZ/IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to VX-445/TEZ/IVA once daily in the morning.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to IVA once daily in the evening.

Arm title	VX-445/TEZ/IVA TC
------------------	-------------------

Arm description:

Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

Arm type	Experimental
Investigational medicinal product name	VX-445/TEZ/IVA
Investigational medicinal product code	VX-445/VX-661/VX-770
Other name	VX-445/Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-445/TEZ/IVA 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]	Placebo	VX-445/TEZ/IVA TC
Started	203	200
Completed	203	197
Not completed	0	3
Other	-	1
Adverse event	-	1
Withdrawal of consent (not due to AE)	-	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: In the above disposition summary, data are presented for 403 subjects who were randomized and dosed in the TC treatment period. Two subjects were enrolled in to the study and randomized but were not dosed in the TC treatment period. Therefore, the total number of enrolled subjects is 405 but the number of subjects reported in subject disposition and baseline is 403.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period.	
Reporting group title	VX-445/TEZ/IVA TC
Reporting group description:	
Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period.	

Reporting group values	Placebo	VX-445/TEZ/IVA TC	Total
Number of subjects	203	200	403
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	26.8	25.6	
standard deviation	± 11.3	± 9.7	-
Gender categorical Units: Subjects			
Female	98	96	194
Male	105	104	209

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period.	
Reporting group title	VX-445/TEZ/IVA TC
Reporting group description: Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period.	

Primary: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)
End point description:	
End point type	Primary
End point timeframe: From Baseline through Week 24	

End point values	Placebo	VX-445/TEZ/IVA TC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	200		
Units: percentage points				
least squares mean (standard error)	-0.4 (± 0.5)	13.9 (± 0.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	VX-445/TEZ/IVA TC v Placebo
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effects model for repeated measure
Parameter estimate	LS Mean Difference
Point estimate	14.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	15.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug in TC treatment period up to 28 days after last dose of study drug or to the completion of study participation date, whichever occurs first

Adverse event reporting additional description:

Adverse events are presented as per Safety Set. Treatment assignments for subjects in the Safety Set are based on actual treatment received, such that all subjects who received at least 1 dose of VX-445/TEZ/IVA TC were included in the VX-445/TEZ/IVA TC group for the safety analysis, even if they were assigned to the placebo group.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects who received placebo matched to VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

Reporting group title	VX-445/TEZ/IVA TC
-----------------------	-------------------

Reporting group description:

Subjects who received VX-445/TEZ/IVA for 24 weeks in the TC treatment period.

Serious adverse events	Placebo	VX-445/TEZ/IVA TC	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 201 (20.90%)	28 / 202 (13.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Axonal neuropathy			

subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroglycopenia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site inflammation			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
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	3 / 201 (1.49%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic paralysis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Painful respiration			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder enlargement			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertransaminaemia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 201 (0.50%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pruritic			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (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			
Acute kidney injury			

subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	33 / 201 (16.42%)	11 / 202 (5.45%)	
occurrences causally related to treatment / all	0 / 44	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 201 (0.00%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial lower respiratory tract infection			

subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coccidioidomycosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes simplex			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sinusitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (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	Placebo	VX-445/TEZ/IVA TC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	180 / 201 (89.55%)	168 / 202 (83.17%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 201 (3.48%)	20 / 202 (9.90%)	
occurrences (all)	8	22	
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 201 (4.48%)	19 / 202 (9.41%)	
occurrences (all)	9	20	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 201 (1.99%)	19 / 202 (9.41%)	
occurrences (all)	4	21	
Bacterial test positive			
subjects affected / exposed	10 / 201 (4.98%)	5 / 202 (2.48%)	
occurrences (all)	13	5	
Blood bilirubin increased			
subjects affected / exposed	2 / 201 (1.00%)	10 / 202 (4.95%)	
occurrences (all)	2	11	
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 201 (14.93%)	35 / 202 (17.33%)	
occurrences (all)	42	49	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 201 (9.45%)	17 / 202 (8.42%)	
occurrences (all)	25	18	
Fatigue			
subjects affected / exposed	20 / 201 (9.95%)	9 / 202 (4.46%)	
occurrences (all)	22	9	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	14 / 201 (6.97%)	26 / 202 (12.87%)	
occurrences (all)	23	32	
Abdominal pain			
subjects affected / exposed	12 / 201 (5.97%)	20 / 202 (9.90%)	
occurrences (all)	20	24	
Nausea			
subjects affected / exposed	14 / 201 (6.97%)	16 / 202 (7.92%)	
occurrences (all)	17	16	
Vomiting			
subjects affected / exposed	10 / 201 (4.98%)	12 / 202 (5.94%)	
occurrences (all)	13	14	
Constipation			
subjects affected / exposed	12 / 201 (5.97%)	6 / 202 (2.97%)	
occurrences (all)	12	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	77 / 201 (38.31%)	34 / 202 (16.83%)	
occurrences (all)	113	39	
Sputum increased			
subjects affected / exposed	39 / 201 (19.40%)	40 / 202 (19.80%)	
occurrences (all)	47	47	
Oropharyngeal pain			
subjects affected / exposed	25 / 201 (12.44%)	20 / 202 (9.90%)	
occurrences (all)	26	27	
Haemoptysis			
subjects affected / exposed	27 / 201 (13.43%)	9 / 202 (4.46%)	
occurrences (all)	39	10	
Nasal congestion			
subjects affected / exposed	15 / 201 (7.46%)	19 / 202 (9.41%)	
occurrences (all)	18	21	
Productive cough			
subjects affected / exposed	16 / 201 (7.96%)	12 / 202 (5.94%)	
occurrences (all)	17	12	
Rhinorrhoea			

subjects affected / exposed occurrences (all)	6 / 201 (2.99%) 7	17 / 202 (8.42%) 19	
Dyspnoea subjects affected / exposed occurrences (all)	13 / 201 (6.47%) 15	5 / 202 (2.48%) 5	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	9 / 201 (4.48%) 11	17 / 202 (8.42%) 20	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	83 / 201 (41.29%) 137	41 / 202 (20.30%) 53	
Nasopharyngitis subjects affected / exposed occurrences (all)	26 / 201 (12.94%) 34	22 / 202 (10.89%) 30	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	22 / 201 (10.95%) 26	24 / 202 (11.88%) 30	
Rhinitis subjects affected / exposed occurrences (all)	11 / 201 (5.47%) 14	15 / 202 (7.43%) 18	
Sinusitis subjects affected / exposed occurrences (all)	8 / 201 (3.98%) 8	11 / 202 (5.45%) 15	
Influenza subjects affected / exposed occurrences (all)	3 / 201 (1.49%) 3	12 / 202 (5.94%) 13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2018	Updated study drug regimen, dosing guidance, dose and population rationale
19 July 2018	Revised exclusion criteria
30 October 2018	A European-specific version of the protocol was created with a 24-week primary endpoint

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported