



## Clinical trial results:

### A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF)

#### Summary

EudraCT number	2017-004132-11
Trial protocol	GB DE DK IE ES PL
Global end of trial date	05 February 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	VX17-659-102
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03447249
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-002191-PIP02-17
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	25 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2019
Global end of trial reached?	Yes
Global end of trial date	05 February 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-659 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	07 March 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: 9
Country: Number of subjects enrolled	United States: 203
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Ireland: 16
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Germany: 51
Worldwide total number of subjects	385
EEA total number of subjects	112

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	94
Adults (18-64 years)	291
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
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<b>Arm title</b>	Placebo
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Arm description:

Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-659/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-659/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.

<b>Arm title</b>	VX-659/TEZ/IVA TC
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Arm description:

Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

Arm type	Experimental
Investigational medicinal product name	VX-659/TEZ/IVA
Investigational medicinal product code	VX-659/VX-661/VX-770
Other name	VX-659/Tezacaftor/Ivacaftor fixed dose combination
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-659/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
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Dosage and administration details:

Subjects received IVA once daily in the evening.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Placebo	VX-659/TEZ/IVA TC
Started	190	192
Completed	185	192
Not completed	5	0
Other	3	-
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 382 subjects who were randomized and dosed in the TC treatment period. Three subjects were enrolled into the study and randomized but were not dosed in the TC treatment period. Therefore, the total number of enrolled subjects is 385 but the number of subjects reported in subject disposition and baseline is 382.

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period.	
Reporting group title	VX-659/TEZ/IVA TC
Reporting group description:	
Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period.	

Reporting group values	Placebo	VX-659/TEZ/IVA TC	Total
Number of subjects	190	192	382
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	27.1 ± 10.0	26.7 ± 9.8	-
Gender categorical Units: Subjects			
Female	83	85	168
Male	107	107	214

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period.	
Reporting group title	VX-659/TEZ/IVA TC
Reporting group description: Subjects who received VX-659/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-659/TEZ/IVA TC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	192		
Units: percentage points				
least squares mean (standard error)	-0.8 (± 0.6)	13.4 (± 0.6)		

### Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	VX-659/TEZ/IVA TC v Placebo
Number of subjects included in analysis	382
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	14.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.6
upper limit	15.7



## 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-659/TEZ/IVA TC were included in the VX-659/TEZ/IVA TC group for the safety analysis, even if they were assigned to the placebo group.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects who received placebo matched to VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

Reporting group title	VX-659/TEZ/IVA TC
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Reporting group description:

Subjects who received VX-659/TEZ/IVA for 24 weeks in the TC treatment period.

Serious adverse events	Placebo	VX-659/TEZ/IVA TC	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 189 (30.69%)	11 / 193 (5.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	3 / 189 (1.59%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (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 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device damage			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			

subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right-to-left cardiac shunt			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (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 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
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	2 / 189 (1.06%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (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			
Axillary mass			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (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			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	45 / 189 (23.81%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	1 / 55	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	2 / 189 (1.06%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 189 (0.00%)	1 / 193 (0.52%)	
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 / 189 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	1 / 189 (0.53%)	0 / 193 (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 %

<b>Non-serious adverse events</b>	Placebo	VX-659/TEZ/IVA TC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 189 (87.83%)	141 / 193 (73.06%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 189 (1.06%)	17 / 193 (8.81%)	
occurrences (all)	3	20	
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 189 (3.70%)	13 / 193 (6.74%)	
occurrences (all)	7	15	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 189 (2.12%)	16 / 193 (8.29%)	
occurrences (all)	5	19	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 189 (16.40%)	26 / 193 (13.47%)	
occurrences (all)	37	30	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 189 (7.94%)	13 / 193 (6.74%)	
occurrences (all)	16	13	
Fatigue			
subjects affected / exposed	19 / 189 (10.05%)	9 / 193 (4.66%)	
occurrences (all)	19	12	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 189 (8.47%)	17 / 193 (8.81%)	
occurrences (all)	21	20	
Abdominal pain upper			

subjects affected / exposed	10 / 189 (5.29%)	3 / 193 (1.55%)	
occurrences (all)	14	3	
Nausea			
subjects affected / exposed	24 / 189 (12.70%)	8 / 193 (4.15%)	
occurrences (all)	31	11	
Vomiting			
subjects affected / exposed	11 / 189 (5.82%)	7 / 193 (3.63%)	
occurrences (all)	11	7	
Constipation			
subjects affected / exposed	5 / 189 (2.65%)	11 / 193 (5.70%)	
occurrences (all)	5	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	68 / 189 (35.98%)	34 / 193 (17.62%)	
occurrences (all)	100	42	
Sputum increased			
subjects affected / exposed	38 / 189 (20.11%)	28 / 193 (14.51%)	
occurrences (all)	43	32	
Oropharyngeal pain			
subjects affected / exposed	13 / 189 (6.88%)	20 / 193 (10.36%)	
occurrences (all)	14	24	
Haemoptysis			
subjects affected / exposed	19 / 189 (10.05%)	6 / 193 (3.11%)	
occurrences (all)	21	6	
Nasal congestion			
subjects affected / exposed	11 / 189 (5.82%)	11 / 193 (5.70%)	
occurrences (all)	11	11	
Productive cough			
subjects affected / exposed	14 / 189 (7.41%)	3 / 193 (1.55%)	
occurrences (all)	22	4	
Respiration abnormal			
subjects affected / exposed	14 / 189 (7.41%)	7 / 193 (3.63%)	
occurrences (all)	16	9	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	10 / 189 (5.29%)	10 / 193 (5.18%)	
occurrences (all)	16	12	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	79 / 189 (41.80%)	21 / 193 (10.88%)	
occurrences (all)	103	23	
Nasopharyngitis			
subjects affected / exposed	16 / 189 (8.47%)	26 / 193 (13.47%)	
occurrences (all)	19	33	
Upper respiratory tract infection			
subjects affected / exposed	7 / 189 (3.70%)	35 / 193 (18.13%)	
occurrences (all)	7	41	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported