

**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 Homozygous for the F508del Mutation (F/F)****Summary**

EudraCT number	2017-004133-82
Trial protocol	IE DE ES GB
Global end of trial date	08 October 2018

Results information

Result version number	v1
This version publication date	17 July 2019
First version publication date	17 July 2019

Trial information**Trial identification**

Sponsor protocol code	VX17-659-103
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03460990
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)	EMEA-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	08 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2018
Global end of trial reached?	Yes
Global end of trial date	08 October 2018
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 homozygous for the F508del mutation (F/F)

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	01 May 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	Australia: 17
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	116
EEA total number of subjects	32

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)	29
Adults (18-64 years)	87

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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Arm title	TEZ/IVA
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Arm description:

Following a run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA for 4 weeks in the TC treatment period.

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

Dosage and administration details:

Subjects received 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.

Arm title	VX-659/TEZ/IVA TC
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Arm description:

Following a run-in period of 4 weeks with TEZ/IVA, subjects received VX-659/TEZ/IVA for 4 weeks in the TC treatment period.

Arm type	Experimental
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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	Placebo (matched to 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 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]	TEZ/IVA	VX-659/TEZ/IVA TC
Started	57	54
Completed	57	54

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 is presented for 111 subjects dosed in the TC treatment period. 5 subjects were included in the run-in period but were not dosed in TC treatment period. Therefore, the total enrolled subjects are 116 whereas the subjects reported in disposition and baseline are 111.

Baseline characteristics

Reporting groups

Reporting group title	TEZ/IVA
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Reporting group description:

Following a run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA for 4 weeks in the TC treatment period.

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

Following a run-in period of 4 weeks with TEZ/IVA, subjects received VX-659/TEZ/IVA for 4 weeks in the TC treatment period.

Reporting group values	TEZ/IVA	VX-659/TEZ/IVA TC	Total
Number of subjects	57	54	111
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	26.2	28.3	
standard deviation	± 9.1	± 9.6	-
Gender categorical Units: Subjects			
Female	33	26	59
Male	24	28	52

End points

End points reporting groups

Reporting group title	TEZ/IVA
Reporting group description: Following a run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA for 4 weeks in the TC treatment period.	
Reporting group title	VX-659/TEZ/IVA TC
Reporting group description: Following a run-in period of 4 weeks with TEZ/IVA, subjects received VX-659/TEZ/IVA for 4 weeks in the TC treatment period.	

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

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)
End point description:	
End point type	Primary
End point timeframe:	At Week 4

End point values	TEZ/IVA	VX-659/TEZ/IVA TC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: percentage points				
least squares mean (standard error)	0.3 (± 0.9)	10.2 (± 0.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	TEZ/IVA v VX-659/TEZ/IVA TC
Number of subjects included in analysis	111
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	10

Confidence interval

level	95 %
sides	2-sided
lower limit	7.4
upper limit	12.5

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	TEZ/IVA
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Reporting group description:

Following a run-in period of 4 weeks with TEZ/IVA, subjects received TEZ/IVA for 4 weeks in the TC treatment period.

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

Following a run-in period of 4 weeks with TEZ/IVA, subjects received VX-659/TEZ/IVA for 4 weeks in the TC treatment period.

Serious adverse events	TEZ/IVA	VX-659/TEZ/IVA TC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 57 (0.00%)	2 / 54 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TEZ/IVA	VX-659/TEZ/IVA TC	
Total subjects affected by non-serious adverse events subjects affected / exposed	19 / 57 (33.33%)	23 / 54 (42.59%)	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	3 / 54 (5.56%) 3	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	3 / 54 (5.56%) 3	
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	4 / 54 (7.41%) 4	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6	3 / 54 (5.56%) 3	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	4 / 54 (7.41%) 4	
Respiratory, thoracic and mediastinal disorders			
Sputum increased subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	9 / 54 (16.67%) 9	
Cough subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3	4 / 54 (7.41%) 4	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 9	2 / 54 (3.70%) 2	

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 and eligibility criteria.
27 April 2018	Revised exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported