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	v2 (current)
This version publication date	26 January 2020
First version publication date	17 July 2019
Version creation reason	• New data added to full data set Addition of Secondary endpoints

Trial information

Trial identification

Sponsor protocol code	VX17-659-103

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
Arm title	TEZ/IVA

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 100 mg/IVA 150 mg 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 150 mg once daily in the evening.

Arm title	VX-659/TEZ/IVA TC

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

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-659 240 mg/TEZ 100 mg/IVA 150 mg 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 150 mg 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
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.	

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
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	56	52	108
Unknown or Not Reported	0	1	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	56	54	110
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Forced Expiratory Volume in 1 Second (ppFEV1)			
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.			
Units: Percentage points			
arithmetic mean	62.9	62.0	
standard deviation	± 14.9	± 14.8	-

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 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:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.	
End point type	Primary
End point timeframe:	
From Baseline 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

Secondary: Absolute Change in Sweat Chloride (SwCl)

End point title	Absolute Change in Sweat Chloride (SwCl)
End point description:	
Sweat samples were collected using an approved collection device.	
End point type	Secondary
End point timeframe:	
From Baseline 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: millimole per liter (mmol/L)				
least squares mean (standard error)	1.5 (± 1.8)	-47.2 (± 1.9)		

Statistical analyses

Statistical analysis title	TEZ/IVA vs VX-659/TEZ/IVA TC
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	-48.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.9
upper limit	-43.5

Secondary: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score

End point title	Absolute Change in Cystic Fibrosis Questionnaire-Revised

	(CFQ-R) Respiratory Domain Score

End point description:

The CFQ-R is a validated participant-reported outcome measuring health-related quality of life for subjects with cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life.

End point type	Secondary

End point timeframe:

From Baseline 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: units on a scale				
least squares mean (standard error)	3.0 (± 1.7)	16.5 (± 1.7)		

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	13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	18.3

Secondary: Safety and Tolerability as Assessed Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Safety and Tolerability as Assessed Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

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 (up to Week 8)

End point values	TEZ/IVA	VX-659/TEZ/IVA TC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: Subjects				
Subjects with AEs	31	33		
Subjects with SAEs	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Pre-Dose Concentration (Ctrough) of VX-659, TEZ, TEZ Metabolite (M1-TEZ), and IVA

End point title	Observed Pre-Dose Concentration (Ctrough) of VX-659, TEZ, TEZ Metabolite (M1-TEZ), and IVA

End point description:

End point type	Secondary

End point timeframe:

From Day 1 and Week 4

End point values	TEZ/IVA	VX-659/TEZ/IVA TC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[1]	54		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1: VX-659 (n= 0, 0)	0 (± 0)	0 (± 0)		
Week 4: VX-659 (n= 0, 52)	99999 (± 99999)	720 (± 589)		
Day 1: TEZ (n= 57, 54)	1780 (± 832)	1590 (± 1020)		
Week 4: TEZ (n= 56, 53)	1730 (± 885)	1280 (± 594)		
Day 1: M1-TEZ (n= 57, 54)	5170 (± 1620)	4840 (± 1860)		
Week 4: M1-TEZ (n= 56, 53)	5010 (± 1810)	4730 (± 1380)		
Day 1: IVA (n= 57, 54)	717 (± 616)	563 (± 400)		
Week 4: IVA (n= 56, 53)	722 (± 642)	401 (± 211)		

Notes:

[1] - "n" in above table signifies subjects evaluable at specified time points and "99999" signifies "NA"

Statistical analyses

No statistical analyses for this end point

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 (up to Week 8)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

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.

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	2 / 57 (3.51%)	3 / 54 (5.56%)	
occurrences (all)	2	3	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
C-reactive protein increased			
subjects affected / exposed	0 / 57 (0.00%)	4 / 54 (7.41%)	
occurrences (all)	0	4	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 57 (8.77%)	3 / 54 (5.56%)	
occurrences (all)	6	3	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 57 (0.00%)	4 / 54 (7.41%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Sputum increased			
subjects affected / exposed	0 / 57 (0.00%)	9 / 54 (16.67%)	
occurrences (all)	0	9	
Cough			
subjects affected / exposed	3 / 57 (5.26%)	4 / 54 (7.41%)	
occurrences (all)	3	4	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	9 / 57 (15.79%)	2 / 54 (3.70%)	
occurrences (all)	9	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