Clinical trial results:
A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-659/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Summary

EudraCT number	2018-001711-67
Trial protocol	Outside EU/EEA
Global end of trial date	18 January 2019

Results information

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

Trial information

Trial identification

Sponsor protocol code	VX18-659-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03633526
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	21 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2019
Global end of trial reached?	Yes
Global end of trial date	18 January 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF).

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	03 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	18
EEA total number of subjects	0

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)	18
Adolescents (12-17 years)	0
Adults (18-64 years)	0
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) 6-11 years of age. The study was terminated before start of Part B at Sponsor's discretion.

Period 1

Period 1 title	Triple Combination Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	VX-659/TEZ/IVA TC

Arm description:

Subjects who received VX-659/TEZ/IVA for 15 days 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

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1[1]	VX-659/TEZ/IVA TC
Started	16
Completed	16

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 16 subjects dosed in the TC treatment period. Two subjects were enrolled but were not dosed in the TC treatment period. Therefore, the total number of enrolled subjects is 18 whereas the number of subjects reported in disposition and baseline is 16.

Baseline characteristics

Reporting groups	
Reporting group title	VX-659/TEZ/IVA TC
Reporting group description:	
Subjects who received VX-659/TEZ/IVA for 15 days in the TC treatment period.	

Reporting group values	VX-659/TEZ/IVA TC	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.2		
standard deviation	± 1.4	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	11	11	

End points

End points reporting groups

Reporting group title	VX-659/TEZ/IVA TC
Reporting group description:	
Subjects who received VX-659/TEZ/IVA for 15 days in the TC treatment period.	

Primary: Maximum Observed Concentration (Cmax) of VX-659, TEZ, and IVA

End point title	Maximum Observed Concentration (Cmax) of VX-659, TEZ, and IVA[1]
End point description:	

End point type	Primary
End point timeframe:	
Day 1 and Day 15	

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 descriptive statistics were planned. No statistical comparisons were planned for primary PK endpoint. PK set included subjects who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "n" signifies those subjects who were evaluable at the specified timepoint.

End point values	VX-659/TEZ/IVA TC			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: microgram per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
VX-659: Day 1 (n=15)	1.81 (± 0.858)			
VX-659: Day 15 (n=15)	2.55 (± 1.21)			
TEZ: Day 1 (n=15)	4.53 (± 1.65)			
TEZ: Day 15 (n=15)	5.22 (± 1.69)			
IVA: Day 1 (n=15)	0.536 (± 0.208)			
IVA: Day 15 (n=15)	0.733 (± 0.256)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Observed Pre-Dose Concentration (Ctrough) of VX-659, TEZ, and IVA[2]
End point description:	

End point type	Primary

End point timeframe:

Day 8 and Day 15

Notes:

[2] - 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 descriptive statistics were planned. No statistical comparisons were planned for primary pharmacokinetic (PK) endpoint. PK set included subjects who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "n" signifies those subjects who were evaluable at the specified timepoint.

End point values	VX-659/TEZ/IVA TC			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: microgram per milliliter (µg/mL)				
arithmetic mean (standard deviation)				
VX-659: Day 8 (n=16)	0.358 (± 0.259)			
VX-659: Day 15 (n=15)	0.367 (± 0.283)			
TEZ: Day 8 (n=16)	0.897 (± 0.488)			
TEZ: Day 15 (n=15)	0.740 (± 0.421)			
IVA: Day 8 (n=16)	0.289 (± 0.195)			
IVA: Day 15 (n=15)	0.283 (± 0.241)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Versus Time Curve from time 0 to 6 Hours (AUC0-6h) of VX-659, TEZ, and IVA

End point title	Area Under the Concentration Versus Time Curve from time 0 to 6 Hours (AUC0-6h) of VX-659, TEZ, and IVA[3]

End point description:

End point type	Primary

End point timeframe:

Day 1 and Day 15

Notes:

[3] - 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 descriptive statistics were planned. No statistical comparisons were planned for primary PK endpoint. PK set included subjects who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "n" signifies those subjects who were evaluable at the specified timepoint.

End point values	VX-659/TEZ/IVA TC			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: hour*microgram per milliliter (h*µg/mL)				
arithmetic mean (standard deviation)				
VX-659: Day 1 (n=15)	5.41 (± 3.65)			
VX-659: Day 15 (n=15)	8.55 (± 4.50)			
TEZ: Day 1 (n=15)	15.5 (± 5.36)			
TEZ: Day 15 (n=15)	19.3 (± 7.26)			
IVA: Day 1 (n=15)	1.64 (± 0.795)			
IVA: Day 15 (n=15)	2.95 (± 1.18)			

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	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	VX-659/TEZ/IVA
Reporting group description: Subjects who received VX-659/TEZ/IVA for 15 days in the TC treatment period.	

Serious adverse events	VX-659/TEZ/IVA		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	VX-659/TEZ/IVA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 16 (81.25%)		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

Bacterial test positive			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Human rhinovirus test positive			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
International normalised ratio increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Pulmonary function test decreased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respirovirus test positive			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Procedural anxiety			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 16 (37.50%)		
occurrences (all)	6		
General disorders and administration site conditions			

Chills			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Post-tussive vomiting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	8		
Nasal discharge discolouration			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Sputum increased			

subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Rash papular subjects affected / exposed occurrences (all) Rash vesicular subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported