Clinical trial results:
A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age

Summary

EudraCT number	2018-001695-38
Trial protocol	GB IE
Global end of trial date	07 August 2020

Results information

Result version number	v1
This version publication date	22 February 2021
First version publication date	22 February 2021

Trial information

Trial identification

Sponsor protocol code	VX18-445-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03691779
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-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	24 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2020
Global end of trial reached?	Yes
Global end of trial date	07 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK), safety and tolerability of elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA) when dosed in triple combination (TC).

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	02 October 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	United Kingdom: 6
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 6
Worldwide total number of subjects	71
EEA total number of subjects	11

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)	71
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 cystic fibrosis (CF) subjects 6 through 11 years of age who were homozygous for F508del [F/F] genotype or heterozygous for F508del and a CFTR minimal function mutation [F/MF] genotypes.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A: ELX/TEZ/IVA

Arm description:

Subjects received ELX/TEZ/IVA in the treatment period for 15 days.

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

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination (FDC) 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	Part B: ELX/TEZ/IVA

Arm description:

Subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.

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

Dosage and administration details:

Subjects received ELX/TEZ/IVA FDC 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	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA
Started	16	66
Completed	16	64
Not completed	0	2
Adverse event	-	1
Withdrawal of consent (not due to AE)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the treatment period for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.	

Reporting group values	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	Total
Number of subjects	16	66	82
Age categorical			
There were 71 unique subjects enrolled in the study. Out of 16 subjects from Part A, 11 subjects also participated in Part B.			
Units: Subjects			
Children (2-11 years)	16	66	71
Gender categorical			
There were 71 unique subjects enrolled in the study. Out of 16 subjects from Part A, 11 subjects also participated in Part B. The total column for gender represents the sum of Part A and Part B numbers as the data for unique 71 subjects was not collected separately.			
Units: Subjects			
Female	11	39	50
Male	5	27	32

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the treatment period for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.	

Primary: Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[1][2]
End point description:	
End point type	Primary
End point timeframe:	
Day 1 through Safety Follow-up Visit (up to Week 28)	

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 this endpoint.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Part B: ELX/TEZ/IVA arm was applicable for this endpoint.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	66			
Units: subjects				
Subjects with TEAEs	65			
Subjects with SAEs	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 Through Safety Follow-up Visit (up to Day 43 for Part A, up to Week 28 for Part B)	
Adverse event reporting additional description:	
MedDRA version for Part A: 21.1, MedDRA version for Part B: 23.0	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1, 23.0

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the treatment period for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the treatment period for 24 weeks.	

Serious adverse events	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Metapneumovirus infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 66 (1.52%)	
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	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)	62 / 66 (93.94%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	7 / 66 (10.61%)	
occurrences (all)	0	9	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Human rhinovirus test positive			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Pulmonary function test decreased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 16 (6.25%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Craniocerebral injury			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 16 (0.00%)	16 / 66 (24.24%)	
occurrences (all)	0	19	
Lethargy			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 16 (0.00%)	5 / 66 (7.58%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	14 / 66 (21.21%)	
occurrences (all)	1	19	
Vessel puncture site pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	8 / 66 (12.12%)	
occurrences (all)	1	9	
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)	5 / 66 (7.58%)	
occurrences (all)	1	5	
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	4 / 66 (6.06%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	7 / 66 (10.61%)	
occurrences (all)	0	8	
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	2 / 66 (3.03%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	7 / 66 (10.61%)	
occurrences (all)	1	10	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	5 / 16 (31.25%)	28 / 66 (42.42%)	
occurrences (all)	5	42	
Nasal congestion			
subjects affected / exposed	2 / 16 (12.50%)	10 / 66 (15.15%)	
occurrences (all)	3	14	
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	12 / 66 (18.18%)	
occurrences (all)	1	14	
Productive cough			
subjects affected / exposed	2 / 16 (12.50%)	5 / 66 (7.58%)	
occurrences (all)	2	5	
Respiration abnormal			
subjects affected / exposed	1 / 16 (6.25%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 16 (6.25%)	8 / 66 (12.12%)	
occurrences (all)	1	9	
Sinus congestion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Sputum increased			
subjects affected / exposed	3 / 16 (18.75%)	3 / 66 (4.55%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Pruritus generalised			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 16 (18.75%)	8 / 66 (12.12%)	
occurrences (all)	3	10	
Rash erythematous			
subjects affected / exposed	1 / 16 (6.25%)	3 / 66 (4.55%)	
occurrences (all)	1	3	
Rash maculo-papular			

subjects affected / exposed	1 / 16 (6.25%)	2 / 66 (3.03%)	
occurrences (all)	1	3	
Rash papular			
subjects affected / exposed	1 / 16 (6.25%)	2 / 66 (3.03%)	
occurrences (all)	1	3	
Infections and infestations			
Croup infectious			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 16 (0.00%)	4 / 66 (6.06%)	
occurrences (all)	0	5	
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	7 / 66 (10.61%)	
occurrences (all)	0	8	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	11 / 66 (16.67%)	
occurrences (all)	0	14	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	8 / 66 (12.12%)	
occurrences (all)	0	8	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 66 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2019	Amended to update secondary endpoints and incorporate dose justification and weight cutoff based on data from Part A.
18 December 2019	Amended to update pre-dose assessment window.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported