Clinical trial results:
A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age

Summary

EudraCT number	2020-002251-38
Trial protocol	DE
Global end of trial date	03 June 2022

Results information

Result version number	v1
This version publication date	17 December 2022
First version publication date	17 December 2022

Trial information

Trial identification

Sponsor protocol code	VX20-445-111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04537793
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 132547

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	21 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2022
Global end of trial reached?	Yes
Global end of trial date	03 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) triple combination therapy in cystic fibrosis (CF) subjects 2 through 5 years of age.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2020
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 States: 49
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 7
Worldwide total number of subjects	83
EEA total number of subjects	7

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)	83
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 CF aged 2 through 5 years of age (inclusive).

Period 1

Period 1 title	Overall Trial (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 morning and IVA in the evening based on their weight at Day 1 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	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination once daily in the morning.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Granules
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 morning and IVA in the evening based on their weight at Day 1 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	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received ELX/TEZ/IVA fixed-dose combination once daily in the morning.

Investigational medicinal product name	IVA
Investigational medicinal product code	VX-770
Other name	Ivacaftor
Pharmaceutical forms	Granules

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	18	75
Completed	18	74
Not completed	0	1
Adverse event	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the morning and IVA in the evening based on their weight at Day 1 for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the morning and IVA in the evening based on their weight at Day 1 for 24 Weeks.	

Reporting group values	Part A: ELX/TEZ/IVA	Part B: ELX/TEZ/IVA	Total
Number of subjects	18	75	93
Age categorical			
There were 83 unique subjects enrolled in the study. Out of 18 subjects from Part A, 10 subjects also participated in Part B.			
Units: Subjects			
Children (2-11 years)	18	75	83
Age continuous			
Units: years			
arithmetic mean	4.3	4.1	
standard deviation	± 0.8	± 1.1	-
Gender categorical			
There were 83 unique subjects enrolled in the study. Out of 18 subjects from Part A, 10 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 83 subjects was not collected separately.			
Units: Subjects			
Female	11	41	52
Male	7	34	41

End points

End points reporting groups

Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the morning and IVA in the evening based on their weight at Day 1 for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the morning and IVA in the evening based on their weight at Day 1 for 24 Weeks.	

Primary: Part A: Observed pre-dose concentration (Ctrough) of ELX, TEZ, IVA, and relevant metabolites

End point title	Part A: Observed pre-dose concentration (Ctrough) of ELX, TEZ, IVA, and relevant metabolites[1][2]
End point description:	
PK set included subjects who received at least 1 dose of study drug. Here "n" signifies those subjects who were evaluable at specified time points for each reporting group respectively.	
End point type	Primary
End point timeframe:	
From Day 1 through 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 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: This primary endpoint is only applicable for Part A.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: micrograms per milliliter (µg/ml)				
arithmetic mean (standard deviation)				
Day 1: ELX (n= 18)	0.00 (± 0.00)			
Day 8: ELX (n= 18)	3.44 (± 2.09)			
Day 15: ELX (n= 17)	3.69 (± 2.11)			
Day 1: ELX-M23 (n= 18)	0.00 (± 0.00)			
Day 8: ELX-M23 (n= 18)	2.39 (± 1.65)			
Day 15: ELX-M23 (n= 17)	2.47 (± 1.65)			
Day 1: IVA (n= 18)	0.00 (± 0.00)			
Day 8: IVA (n= 18)	0.702 (± 0.503)			
Day 15: IVA (n= 17)	0.746 (± 0.526)			
Day 1: IVA-M1 (n= 18)	0.00 (± 0.00)			
Day 8: IVA-M1 (n= 18)	1.78 (± 0.990)			
Day 15: IVA-M1 (n= 17)	1.91 (± 0.990)			
Day 1: TEZ (n= 18)	0.00 (± 0.00)			

Day 8: TEZ (n= 18)	1.86 (± 1.07)			
Day 15: TEZ (n= 17)	1.85 (± 1.10)			
Day 1: TEZ-M1 (n= 18)	0.00 (± 0.00)			
Day 8: TEZ-M1 (n= 18)	6.42 (± 1.42)			
Day 15: TEZ-M1 (n= 17)	7.68 (± 1.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse

End point title	Part A : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse[3][4]

End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

End point type	Primary

End point timeframe:

From Day 1 up to Day 43

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 this endpoint.
[4] - 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: This primary endpoint is only applicable for Part A.

End point values	Part A: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Subjects				
Subjects with TEAEs	15			
Subjects with SAEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent

End point title	Part B : Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent[5][6]

End point description:

Safety set included all subjects who received at least 1 dose of study drug in the treatment period.

End point type	Primary

End point timeframe:

From Day 1 up to Week 28

Notes:

[5] - 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.
[6] - 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: This primary endpoint is only applicable for Part B.

End point values	Part B: ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Subjects				
Subjects with TEAEs	74			
Subjects with SAEs	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Day 1 Through Safety Follow-up Period (up to Day 43 for Part A and up to Week 28 for Part B)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Part A: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the morning and IVA in the evening based on their weight at Day 1 for 15 days.	
Reporting group title	Part B: ELX/TEZ/IVA
Reporting group description:	
Subjects received ELX/TEZ/IVA in the morning and IVA in the evening based on their weight at Day 1 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 / 18 (0.00%)	2 / 75 (2.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Anal incontinence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 75 (1.33%)	
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	15 / 18 (83.33%)	71 / 75 (94.67%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 18 (16.67%)	8 / 75 (10.67%)	
occurrences (all)	3	9	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	4 / 75 (5.33%)	
occurrences (all)	2	7	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 18 (5.56%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 18 (0.00%)	7 / 75 (9.33%)	
occurrences (all)	0	7	
Injury, poisoning and procedural complications			
Scratch			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 18 (0.00%)	7 / 75 (9.33%)	
occurrences (all)	0	7	
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	26 / 75 (34.67%)	
occurrences (all)	1	33	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 18 (0.00%)	5 / 75 (6.67%)	
occurrences (all)	0	6	
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	4 / 75 (5.33%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	1 / 18 (5.56%)	6 / 75 (8.00%)	
occurrences (all)	1	6	
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	21 / 75 (28.00%)	
occurrences (all)	0	25	
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	5 / 75 (6.67%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 18 (22.22%)	46 / 75 (61.33%)	
occurrences (all)	4	84	
Nasal congestion			
subjects affected / exposed	0 / 18 (0.00%)	13 / 75 (17.33%)	
occurrences (all)	0	18	
Productive cough			
subjects affected / exposed	1 / 18 (5.56%)	3 / 75 (4.00%)	
occurrences (all)	1	3	
Rhinorrhoea			
subjects affected / exposed	3 / 18 (16.67%)	25 / 75 (33.33%)	
occurrences (all)	4	34	
Sputum increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 18 (5.56%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	2 / 18 (11.11%)	12 / 75 (16.00%)	
occurrences (all)	4	14	
Rash erythematous			
subjects affected / exposed	1 / 18 (5.56%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 18 (5.56%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 18 (0.00%)	4 / 75 (5.33%)	
occurrences (all)	0	4	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 18 (0.00%)	14 / 75 (18.67%)	
occurrences (all)	0	14	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 18 (0.00%)	8 / 75 (10.67%)	
occurrences (all)	0	8	
Upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	11 / 75 (14.67%)	
occurrences (all)	1	13	
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	6 / 75 (8.00%)	
occurrences (all)	0	13	
Product issues			
Product taste abnormal			

subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	9 / 75 (12.00%)	
occurrences (all)	0	9	
Hyperamylasaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Hyperlipasaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 75 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2021	Updated the dose in Part B; Updated the sample size for subjects between 2 and 3 years of age (inclusive) in Part B; Added guidance for blood draws; Updated exclusion criterion to avoid enrolling subjects with liver function test (LFT) abnormalities in the previous year in the study.
21 October 2021	Amended to expand the study population to include subjects who have at least 1 F508del mutation in the CFTR gene or an ELX/TEZ/IVA-responsive CFTR mutation in part B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported