Clinical trial results:
A Phase 3b, Randomized, Double blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del

Summary

EudraCT number	2019-001735-31
Trial protocol	GB BE
Global end of trial date	24 July 2020

Results information

Result version number	v2 (current)
This version publication date	04 September 2021
First version publication date	06 February 2021
Version creation reason	• New data added to full data set Addition of secondary endpoints

Trial information

Trial identification

Sponsor protocol code	VX18-445-109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04105972
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)	No
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	11 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2020
Global end of trial reached?	Yes
Global end of trial date	24 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-445/TEZ/IVA in cystic fibrosis subjects, homozygous for F508del (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	03 October 2019
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 Kingdom: 88
Country: Number of subjects enrolled	Australia: 30
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Germany: 38
Worldwide total number of subjects	176
EEA total number of subjects	146

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)	53
Adults (18-64 years)	123
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 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 TEZ/IVA run-in period of 4 weeks, subjects received TEZ 100 milligrams (mg) once daily (qd)/IVA 150 mg every 12 hours (q12h) in the treatment period for 24 weeks.

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

Dosage and administration details:

Subjects received 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	ELX/TEZ/IVA

Arm description:

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h 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[1]	TEZ/IVA	ELX/TEZ/IVA
Started	88	87
Completed	86	86
Not completed	2	1
Adverse Event	2	1

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: A total of 176 subjects enrolled in the study. Out of those 176 subjects, 1 subject was randomized but not dosed in the treatment period.
Therefore, only 175 subjects are included in the subject disposition and baseline section.

Baseline characteristics

Reporting groups	
Reporting group title	TEZ/IVA
Reporting group description:	
Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ 100 milligrams (mg) once daily (qd)/IVA 150 mg every 12 hours (q12h) in the treatment period for 24 weeks.	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Following TEZ/IVA run-in period of 4 weeks, subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.	

Reporting group values	TEZ/IVA	ELX/TEZ/IVA	Total
Number of subjects	88	87	175
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	27.8	27.9	
standard deviation	± 11.0	± 11.8	-
Gender categorical Units: Subjects			
Female	45	43	88
Male	43	44	87
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	83	85	168
Unknown or Not Reported	3	1	4
Ethnicity/Race Units: Subjects			
Asian	0	2	2
White	88	84	172
White, Asian	0	1	1
CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score			
The CFQ-R is a validated subject-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.			
Units: units on a scale			
arithmetic mean	73.1	71.2	
standard deviation	± 17.6	± 19.6	-

End points

End points reporting groups

Reporting group title	TEZ/IVA
Reporting group description:	
Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ 100 milligrams (mg) once daily (qd)/IVA 150 mg every 12 hours (q12h) in the treatment period for 24 weeks.	
Reporting group title	ELX/TEZ/IVA
Reporting group description:	
Following TEZ/IVA run-in period of 4 weeks, subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.	

Primary: Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score

End point title	Absolute Change in CF Questionnaire-Revised (CFQ-R) Respiratory Domain Score
End point description:	
The CFQ-R is a validated subject-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. Full analysis set (FAS) included all randomized subjects who carried the intended CF transmembrane conductance regulator (CFTR) allele mutation and received at least 1 dose of study drug in treatment period.	
End point type	Primary
End point timeframe:	
From Baseline Through Week 24	

End point values	TEZ/IVA	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	87		
Units: units on scale				
least squares mean (standard error)	1.2 (± 1.5)	17.1 (± 1.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	ELX/TEZ/IVA v TEZ/IVA
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effects Model for Repeated Measure
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	15.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	20.1

Secondary: 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. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 24

End point values	TEZ/IVA	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	87		
Units: percentage points				
least squares mean (standard error)	1.0 (± 0.7)	11.2 (± 0.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	TEZ/IVA v ELX/TEZ/IVA
Number of subjects included in analysis	175
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	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.2
upper limit	12.1

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. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 24

End point values	TEZ/IVA	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	87		
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	-3.4 (± 1.2)	-46.2 (± 1.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	TEZ/IVA v ELX/TEZ/IVA
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-42.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.2
upper limit	-39.3

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Day 1 in the Treatment Period up to 28 Days After the Last Dose of Study Drug or to the Completion of Study Participation Date, Whichever Occurs First (up to Week 28)

End point values	TEZ/IVA	ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	87		
Units: subjects				
Subjects With TEAEs	81	77		
Subjects With SAEs	14	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 in the 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 28)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	TEZ/IVA

Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.

Reporting group title	ELX/TEZ/IVA

Reporting group description:

Following TEZ/IVA run-in period of 4 weeks, subjects received ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 24 weeks.

Serious adverse events	TEZ/IVA	ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 88 (15.91%)	5 / 87 (5.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 88 (1.14%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obsessive-compulsive disorder			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
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	9 / 88 (10.23%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 88 (1.14%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 3 diabetes mellitus			
subjects affected / exposed	0 / 88 (0.00%)	1 / 87 (1.15%)	
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	ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 88 (81.82%)	59 / 87 (67.82%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 88 (1.14%)	6 / 87 (6.90%)	
occurrences (all)	2	7	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 88 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	6	
Bacterial test positive			
subjects affected / exposed	5 / 88 (5.68%)	1 / 87 (1.15%)	
occurrences (all)	8	1	
Nervous system disorders			

Headache			
subjects affected / exposed	18 / 88 (20.45%)	25 / 87 (28.74%)	
occurrences (all)	26	38	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 88 (7.95%)	4 / 87 (4.60%)	
occurrences (all)	10	6	
Diarrhoea			
subjects affected / exposed	7 / 88 (7.95%)	8 / 87 (9.20%)	
occurrences (all)	8	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 88 (26.14%)	11 / 87 (12.64%)	
occurrences (all)	32	17	
Haemoptysis			
subjects affected / exposed	6 / 88 (6.82%)	3 / 87 (3.45%)	
occurrences (all)	8	3	
Nasal congestion			
subjects affected / exposed	0 / 88 (0.00%)	6 / 87 (6.90%)	
occurrences (all)	0	6	
Oropharyngeal pain			
subjects affected / exposed	7 / 88 (7.95%)	11 / 87 (12.64%)	
occurrences (all)	8	12	
Productive cough			
subjects affected / exposed	3 / 88 (3.41%)	8 / 87 (9.20%)	
occurrences (all)	4	10	
Sputum increased			
subjects affected / exposed	16 / 88 (18.18%)	10 / 87 (11.49%)	
occurrences (all)	18	10	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 88 (0.00%)	7 / 87 (8.05%)	
occurrences (all)	0	8	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	32 / 88 (36.36%)	10 / 87 (11.49%)	
occurrences (all)	38	12	
Nasopharyngitis			
subjects affected / exposed	13 / 88 (14.77%)	17 / 87 (19.54%)	
occurrences (all)	18	19	
Upper respiratory tract infection			
subjects affected / exposed	5 / 88 (5.68%)	9 / 87 (10.34%)	
occurrences (all)	6	11	

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