Clinical trial results:
A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

Summary

EudraCT number	2018-002835-76
Trial protocol	GB IE DE DK FR BE NL IT
Global end of trial date	12 June 2020

Results information

Result version number	v2 (current)
This version publication date	22 July 2021
First version publication date	26 December 2020
Version creation reason	• New data added to full data set Addition of secondary endpoints

Trial information

Trial identification

Sponsor protocol code	VX18-445-104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04058353
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	30 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2020
Global end of trial reached?	Yes
Global end of trial date	12 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in cystic fibrosis (CF) subjects who are heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes).

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	28 August 2019
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: 92
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Denmark: 2
Worldwide total number of subjects	271
EEA total number of subjects	140

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)	24
Adults (18-64 years)	242
From 65 to 84 years	5
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	Control: IVA or TEZ/IVA

Arm description:

Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA 150 milligrams (mg) every 12 hours (q12h) or TEZ 100 mg once daily (qd)/IVA 150 mg q12h in the treatment period for 8 weeks.

Arm type	Active comparator
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 every 12 hours.

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 once daily and IVA every 12 hours.

Arm title	Triple Combination (TC): ELX/TEZ/IVA

Arm description:

Following an IVA or 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 8 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 VX-445/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	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]	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA
Started	126	132
Completed	122	131
Not completed	4	1
Physician decision	1	-
Other	1	-
Adverse event	2	-
Adverse Events	-	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 271 subjects enrolled, 12 subjects discontinued in run-in period of the study. Of 259 subjects, 1 subject randomized but not dosed in
the treatment period. Therefore, only 258 subjects are included in the subject disposition and baseline sections.

Baseline characteristics

Reporting groups	
Reporting group title	Control: IVA or TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA 150 milligrams (mg) every 12 hours (q12h) or TEZ 100 mg once daily (qd)/IVA 150 mg q12h in the treatment period for 8 weeks.	
Reporting group title	Triple Combination (TC): ELX/TEZ/IVA
Reporting group description:	
Following an IVA or 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 8 weeks.	

Reporting group values	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA	Total
Number of subjects	126	132	258
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	37.6	37.7	
standard deviation	± 14.3	± 14.7	-
Gender categorical Units: Subjects			
Female	61	67	128
Male	65	65	130
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	5	9
Not Hispanic or Latino	114	117	231
Unknown or Not Reported	8	10	18
Race/Ethnicity Units: Subjects			
Black or African American	2	0	2
Not Collected per Local Regulations	9	9	18
Aboriginal	2	1	3
Latin-American	1	0	1
Lebanese	1	0	1
White	110	122	232
White, American Indian or Alaska Native	1	0	1
Percent Predicted 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	68.1	67.1	
standard deviation	± 16.4	± 15.7	-

End points

End points reporting groups

Reporting group title	Control: IVA or TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA 150 milligrams (mg) every 12 hours (q12h) or TEZ 100 mg once daily (qd)/IVA 150 mg q12h in the treatment period for 8 weeks.	
Reporting group title	Triple Combination (TC): ELX/TEZ/IVA
Reporting group description:	
Following an IVA or 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 8 weeks.	

Primary: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for the ELX/TEZ/IVA Group

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for the ELX/TEZ/IVA Group[1][2]
End point description:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Full analysis set (FAS) included all randomized subjects who have the intended CF transmembrane conductance regulator (CFTR) allele mutation and received at least 1 dose of study drug in the treatment period.	
End point type	Primary
End point timeframe:	
From Baseline Through Week 8	

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 within treatment group comparison was planned for this endpoint. Individual within-group comparison cannot be reported in the EudraCT
database. Therefore, no statistical comparisons were reported.
[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 endpoint was applicable only for the triple combination arm.

End point values	Triple Combination (TC): ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: percentage points				
least squares mean (confidence interval 95%)	3.7 (2.8 to 4.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Sweat Chloride (SwCl) for ELX/TEZ/IVA Group

End point title	Absolute Change in Sweat Chloride (SwCl) for ELX/TEZ/IVA Group[3]

End point description:

Sweat samples were collected using an approved collection device. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 8

Notes:

[3] - 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 endpoint was applicable only for the triple combination arm.

End point values	Triple Combination (TC): ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: millimole per liter (mmol/L)				
least squares mean (confidence interval 95%)	-22.3 (-24.5 to -20.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in ppFEV1 for the ELX/TEZ/IVA Group Compared to the Control Group

End point title	Absolute Change in ppFEV1 for the ELX/TEZ/IVA Group Compared to the Control Group

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 8

End point values	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	132		
Units: percentage points				
least squares mean (confidence interval 95%)	0.2 (-0.7 to 1.1)	3.7 (2.8 to 4.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Control: IVA or TEZ/IVA v Triple Combination (TC): ELX/TEZ/IVA
Number of subjects included in analysis	258
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	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	4.7

Secondary: Absolute Change in SwCl for ELX/TEZ/IVA Group Compared to the Control Group

End point title	Absolute Change in SwCl for ELX/TEZ/IVA Group Compared to the Control Group
End point description:	
Sweat samples were collected using an approved collection device. FAS.	
End point type	Secondary
End point timeframe:	
From Baseline Through Week 8	

End point values	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	132		
Units: mmol/L				
least squares mean (confidence interval 95%)	0.7 (-1.4 to 2.8)	-22.3 (-24.5 to -20.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Control: IVA or TEZ/IVA v Triple Combination (TC): ELX/TEZ/IVA

Number of subjects included in analysis	258
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	-23.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.1
upper limit	-20.1

Secondary: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for ELX/TEZ/IVA Group

End point title	Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for ELX/TEZ/IVA Group[4]

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. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 8

Notes:

[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 endpoint was applicable only for the triple combination arm.

End point values	Triple Combination (TC): ELX/TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	132			
Units: units on a scale				
least squares mean (confidence interval 95%)	10.3 (8.0 to 12.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in CFQ-R Respiratory Domain Score for ELX/TEZ/IVA Group Compared to the Control Group

End point title	Absolute Change in CFQ-R Respiratory Domain Score for ELX/TEZ/IVA Group Compared to the Control Group

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. FAS.

End point type	Secondary

End point timeframe:

From Baseline Through Week 8

End point values	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	132		
Units: units on a scale				
least squares mean (confidence interval 95%)	1.6 (-0.8 to 4.1)	10.3 (8.0 to 12.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Control: IVA or TEZ/IVA v Triple Combination (TC): ELX/TEZ/IVA
Number of subjects included in analysis	258
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	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	12.1

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:

Day 1 up to Week 12

End point values	Control: IVA or TEZ/IVA	Triple Combination (TC): ELX/TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	132		
Units: subjects				
Subjects With TEAEs	83	88		
Subjects With SAEs	11	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Control: IVA or TEZ/IVA
Reporting group description:	
Following an IVA or TEZ/IVA run-in period of 4 weeks, subjects either received IVA 150 mg q12h or TEZ 100 mg qd/IVA 150 mg q12h in the treatment period for 8 weeks.	
Reporting group title	TC: ELX/TEZ/IVA
Reporting group description:	
Following an IVA or 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 8 weeks.	

Serious adverse events	Control: IVA or TEZ/IVA	TC: ELX/TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 126 (8.73%)	5 / 132 (3.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 126 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	7 / 126 (5.56%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control: IVA or TEZ/IVA	TC: ELX/TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 126 (37.30%)	35 / 132 (26.52%)	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 126 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	9	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 126 (0.00%)	8 / 132 (6.06%)	
occurrences (all)	0	8	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 126 (15.08%)	11 / 132 (8.33%)	
occurrences (all)	30	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 126 (1.59%)	7 / 132 (5.30%)	
occurrences (all)	2	7	
Diarrhoea			
subjects affected / exposed	8 / 126 (6.35%)	5 / 132 (3.79%)	
occurrences (all)	13	5	
Nausea			
subjects affected / exposed	9 / 126 (7.14%)	2 / 132 (1.52%)	
occurrences (all)	16	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 126 (14.29%)	3 / 132 (2.27%)	
occurrences (all)	21	3	
Sputum increased			
subjects affected / exposed	8 / 126 (6.35%)	6 / 132 (4.55%)	
occurrences (all)	8	6	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	10 / 126 (7.94%)	2 / 132 (1.52%)	
occurrences (all)	11	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2019	Amended to add an exploratory endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported