Clinical trial results:
A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2019-002189-11
Trial protocol	Outside EU/EEA
Global end of trial date	24 July 2018

Results information

Result version number	v1 (current)
This version publication date	07 November 2019
First version publication date	07 November 2019

Trial information

Trial identification

Sponsor protocol code	VX15-661-112

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02730208
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	23 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2018
Global end of trial reached?	Yes
Global end of trial date	24 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the treatment effect of tezacaftor in combination with ivacaftor (TEZ/IVA) on chest imaging endpoints using low-dose computed tomography (LDCT) at Week 72, and to evaluate the safety of TEZ/IVA through Week 72.

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	13 September 2016
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	Australia: 41
Worldwide total number of subjects	41
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)	0
Adolescents (12-17 years)	19
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 41 subjects were randomized and treated in the study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	TEZ/IVA

Arm description:

Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks.

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

Dosage and administration details:

Subjects received TEZ 100 milligram (mg)/IVA 150 mg once daily.

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 150 mg once daily.

Arm title	Placebo

Arm description:

Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to TEZ/IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to TEZ/IVA once daily.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to IVA once daily.

Number of subjects in period 1	TEZ/IVA	Placebo
Started	20	21
Completed	20	20
Not completed	0	1
Withdrawal of consent (not due to AE)	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks.	

Reporting group values	TEZ/IVA	Placebo	Total
Number of subjects	20	21	41
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	20.4	20.1	
standard deviation	± 7.5	± 9.3	-
Gender categorical Units: Subjects			
Female	11	10	21
Male	9	11	20
Ethnicity (NIH/ OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	20	21	41
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	20	21	41
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Total Brody/ Cystic Fibrosis - Computed Tomography (CFCT) Score			
The exploratory Brody/CF-CT score semi-quantitatively scores the degree of structural lung disease as shown on CT in subjects with CF. The score ranges from a minimum of 0 to a maximum of 219 with higher scores indicating more severe structural lung disease.			
Units: scores on a scale			
arithmetic mean	38.29	43.68	
standard deviation	± 22.91	± 33.96	-

End points

End points reporting groups

Reporting group title	TEZ/IVA
Reporting group description:	
Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks.	

Primary: Absolute Change in Total Brody/CF-CT Score

End point title	Absolute Change in Total Brody/CF-CT Score
End point description:	
The exploratory Brody/CF-CT score semi-quantitatively scores the degree of structural lung disease as shown on CT in subjects with CF. The score ranges from a minimum of 0 to a maximum of 219 with higher scores indicating more severe structural lung disease. The full analysis set (FAS) included all subjects who were randomized and received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
From Baseline at Week 72	

End point values	TEZ/IVA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: scores on a scale				
least squares mean (standard error)	0.90 (± 2.09)	2.38 (± 2.07)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	TEZ/IVA v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.47
upper limit	4.52

Notes:

[1] - Treatment effect outcomes are estimates.

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

The safety set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 1 up to Week 76

End point values	TEZ/IVA	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: Subjects				
Subjects with AEs	20	21		
Subjects with SAEs	8	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 76	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects received TEZ/IVA fixed dose combination in the morning and IVA in the evening for 72 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to TEZ/IVA fixed dose combination in the morning and placebo matched to IVA in the evening for 72 weeks.	

Serious adverse events	TEZ/IVA	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)	13 / 21 (61.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Bacterial test positive			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Type I hypersensitivity			

subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
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	5 / 20 (25.00%)	6 / 21 (28.57%)	
occurrences causally related to treatment / all	0 / 7	1 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	
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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)	20 / 21 (95.24%)	
Investigations			

Bacterial test positive			
subjects affected / exposed	0 / 20 (0.00%)	5 / 21 (23.81%)	
occurrences (all)	0	8	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Fungal test positive			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Sunburn			
subjects affected / exposed	1 / 20 (5.00%)	3 / 21 (14.29%)	
occurrences (all)	1	3	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)	4 / 21 (19.05%)	
occurrences (all)	1	9	
Migraine			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	6	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	3 / 20 (15.00%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	2	3	
Constipation			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	4 / 21 (19.05%)	
occurrences (all)	0	8	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 20 (40.00%)	9 / 21 (42.86%)	
occurrences (all)	9	12	
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	4	
Haemoptysis			
subjects affected / exposed	4 / 20 (20.00%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
Oropharyngeal pain			
subjects affected / exposed	2 / 20 (10.00%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Productive cough			
subjects affected / exposed	4 / 20 (20.00%)	4 / 21 (19.05%)	
occurrences (all)	5	7	
Rhinorrhoea			
subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Sputum increased			
subjects affected / exposed	2 / 20 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Upper respiratory tract congestion			

subjects affected / exposed	1 / 20 (5.00%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	5 / 20 (25.00%)	9 / 21 (42.86%)	
occurrences (all)	12	16	
Influenza			
subjects affected / exposed	2 / 20 (10.00%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Lower respiratory tract infection bacterial			
subjects affected / exposed	3 / 20 (15.00%)	2 / 21 (9.52%)	
occurrences (all)	5	3	
Nasopharyngitis			
subjects affected / exposed	3 / 20 (15.00%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Pharyngitis			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	4 / 20 (20.00%)	2 / 21 (9.52%)	
occurrences (all)	5	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2016	Clarified assessment requirements and analysis timing
15 December 2016	Removed interim analysis, revised assessments, clarified eligibility requirements
24 October 2017	Clarified visit requirements
26 February 2018	Clarified visit requirements, added endpoint

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported