Clinical trial results:
Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2017-000540-18
Trial protocol	FR DE
Global end of trial date	09 August 2018

Results information

Result version number	v2 (current)
This version publication date	03 January 2020
First version publication date	24 February 2019
Version creation reason	• New data added to full data set Addition of Secondary Endpoints

Trial information

Trial identification

Sponsor protocol code	VX16-661-114

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03150719
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, 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	27 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 August 2018
Global end of trial reached?	Yes
Global end of trial date	09 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the respiratory safety of Tezacaftor/Ivacaftor (TEZ/IVA) in subjects with Cystic Fibrosis homozygous for F508del mutation of the CFTR gene that previously discontinued Lumacaftor/Ivacaftor (LUM/IVA) due to treatment-related respiratory signs or symptoms

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	24 May 2017
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	France: 12
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	98
EEA total number of subjects	49

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)	1
Adults (18-64 years)	97
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 98 subjects were randomized: 47 in placebo group and 51 in TEZ/IVA group. One subject in TEZ/IVA group did not receive any study drug.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to TEZ/IVA fixed dose combination (FDC) once daily in the morning followed by placebo matched to IVA once daily in the evening for 56 days.

Arm type	Experimental
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 FDC once daily in the morning for 56 days.

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 in the evening for 56 days.

Arm title	TEZ/IVA

Arm description:

Subjects received TEZ/IVA FDC once daily in the morning followed by IVA once daily in the evening for 56 days.

Arm type	Experimental
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 100 milligram (mg) TEZ/ 150 mg IVA FDC once daily in the morning for 56 days.

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 150 mg IVA once daily in the evening for 56 days.

Number of subjects in period 1[1]	Placebo	TEZ/IVA
Started	47	50
Completed	46	48
Not completed	1	2
Adverse Event	-	1
Other	1	-
Death	-	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 98 subjects were randomized: 47 in placebo group and 51 in TEZ/IVA group. One subject in TEZ/IVA group did not receive any study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to TEZ/IVA fixed dose combination (FDC) once daily in the morning followed by placebo matched to IVA once daily in the evening for 56 days.	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects received TEZ/IVA FDC once daily in the morning followed by IVA once daily in the evening for 56 days.	

Reporting group values	Placebo	TEZ/IVA	Total
Number of subjects	47	50	97
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.3	34.3	
standard deviation	± 10.0	± 8.7	-
Gender categorical Units: Subjects			
Female	30	31	61
Male	17	19	36
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	1	4
Not Hispanic or Latino	40	41	81
Unknown or Not Reported	4	8	12
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	1	0	1
White	42	42	84
More than one race	0	0	0
Unknown or Not Reported	4	8	12

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to TEZ/IVA fixed dose combination (FDC) once daily in the morning followed by placebo matched to IVA once daily in the evening for 56 days.	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects received TEZ/IVA FDC once daily in the morning followed by IVA once daily in the evening for 56 days.	

Primary: Incidence of Respiratory Adverse Events of Special Interest (RAESIs)

End point title	Incidence of Respiratory Adverse Events of Special Interest (RAESIs)[1]
End point description:	
RAESIs included chest discomfort, dyspnea (shortness of breath), respiration abnormal (chest tightness), asthma, bronchial hyperreactivity, bronchospasm, and wheezing.	
End point type	Primary
End point timeframe:	
Day 1 up to Day 84	

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 primary safety endpoint.

End point values	Placebo	TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: Subjects	10	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Average of Day 28 and Day 56 Measurements

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) at Average of Day 28 and Day 56 Measurements
End point description:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.	
End point type	Secondary
End point timeframe:	
Baseline, Day 28 and Day 56	

End point values	Placebo	TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: percent predicted of FEV1				
arithmetic mean (standard deviation)	-0.6 (± 3.4)	2.2 (± 4.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	TEZ/IVA v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean Difference
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4.4

Secondary: Relative Change From Baseline in ppFEV1 at Average of Day 28 and Day 56 Measurements

End point title	Relative Change From Baseline in ppFEV1 at Average of Day 28 and Day 56 Measurements
End point description:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.	
End point type	Secondary
End point timeframe:	
Baseline, Day 28 and Day 56	

End point values	Placebo	TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: percent change				
arithmetic mean (standard deviation)	-1.5 (± 8.1)	5.2 (± 12.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v TEZ/IVA
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean Difference
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	10.9

Secondary: Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score at Average of Day 28 and Day 56 Measurements

End point title	Absolute Change From Baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score at Average of Day 28 and Day 56 Measurements

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.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 56

End point values	Placebo	TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: units on a scale				
arithmetic mean (standard deviation)	4.7 (± 15.4)	5.7 (± 14.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo v TEZ/IVA
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean Difference
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	7

Secondary: Tolerability as Assessed by Number of Subjects Who Discontinued Treatment

End point title	Tolerability as Assessed by Number of Subjects Who Discontinued Treatment

End point description:

End point type	Secondary

End point timeframe:

Day 1 through Day 56

End point values	Placebo	TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: subjects	2	2		

Statistical analyses

No statistical analyses for this end point

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:

End point type	Secondary

End point timeframe:

Day 1 up to Day 84

End point values	Placebo	TEZ/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: subjects				
Subjects with AEs	39	37		
Subjects with SAEs	9	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 84

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to TEZ/IVA fixed dose combination (FDC) once daily in the morning followed by placebo matched to IVA once daily in the evening for 56 days.

Reporting group title	TEZ/IVA

Reporting group description:

Subjects received TEZ/IVA FDC once daily in the morning followed by IVA once daily in the evening for 56 days.

Serious adverse events	Placebo	TEZ/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 47 (19.15%)	5 / 50 (10.00%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
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			
Pleuritic pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (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			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	7 / 47 (14.89%)	3 / 50 (6.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 50 (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	Placebo	TEZ/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 47 (59.57%)	30 / 50 (60.00%)	
Investigations			
Bacterial test positive			
subjects affected / exposed	0 / 47 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 47 (14.89%)	6 / 50 (12.00%)	
occurrences (all)	11	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 47 (8.51%)	2 / 50 (4.00%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 47 (10.64%)	4 / 50 (8.00%)	
occurrences (all)	9	4	
Constipation			
subjects affected / exposed	0 / 47 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	2 / 47 (4.26%)	4 / 50 (8.00%)	
occurrences (all)	2	5	
Diarrhoea			
subjects affected / exposed	3 / 47 (6.38%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 47 (17.02%)	9 / 50 (18.00%)	
occurrences (all)	8	9	
Dyspnoea			
subjects affected / exposed	5 / 47 (10.64%)	5 / 50 (10.00%)	
occurrences (all)	5	5	
Haemoptysis			

subjects affected / exposed	2 / 47 (4.26%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Respiration abnormal			
subjects affected / exposed	1 / 47 (2.13%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Oropharyngeal pain			
subjects affected / exposed	3 / 47 (6.38%)	2 / 50 (4.00%)	
occurrences (all)	3	2	
Sputum increased			
subjects affected / exposed	5 / 47 (10.64%)	2 / 50 (4.00%)	
occurrences (all)	5	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 47 (0.00%)	6 / 50 (12.00%)	
occurrences (all)	0	6	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	9 / 47 (19.15%)	4 / 50 (8.00%)	
occurrences (all)	10	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 47 (6.38%)	1 / 50 (2.00%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2017	Revised sample size, and the time from Orkambi initiation to discontinuation; Additional safety measures added; Subjects who completed Day 56 Visit were given the opportunity to enroll in a long-term, open-label safety study of TEZ/IVA
09 June 2017	Added post-dose spirometry on Day 1 for additional safety; Clarified the visits for pulse oximetry and vital sign assessments; Removed restrictions on the concomitant use of corticosteroids

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported