



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	v1
This version publication date	24 February 2019
First version publication date	24 February 2019

Trial information

Trial identification

Sponsor protocol code	VX16-661-114
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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 8776348789, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 8776348789, 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

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
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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
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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
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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

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:	
End point type	Primary
End point timeframe: Day 1 up to Day 56	
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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 84

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Placebo
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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
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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 occurrences (all)	0 / 47 (0.00%) 0	3 / 50 (6.00%) 3	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	7 / 47 (14.89%) 11	6 / 50 (12.00%) 6	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 4	2 / 50 (4.00%) 2	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 9 0 / 47 (0.00%) 0 2 / 47 (4.26%) 2 3 / 47 (6.38%) 3	4 / 50 (8.00%) 4 4 / 50 (8.00%) 4 4 / 50 (8.00%) 5 1 / 50 (2.00%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Haemoptysis	8 / 47 (17.02%) 8 5 / 47 (10.64%) 5	9 / 50 (18.00%) 9 5 / 50 (10.00%) 5	

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