Clinical trial results:
A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation

Summary

EudraCT number	2016-004479-35
Trial protocol	IE DK BE DE GB PL FR
Global end of trial date	21 December 2018

Results information

Result version number	v2 (current)
This version publication date	29 April 2020
First version publication date	09 July 2019
Version creation reason	• New data added to full data set Update for Consistency with CT.gov results

Trial information

Trial identification

Sponsor protocol code	VX16-661-115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03559062
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001640-PIP01-14
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	01 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2018
Global end of trial reached?	Yes
Global end of trial date	21 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of tezacaftor (TEZ) in combination with ivacaftor (IVA) in subjects with cystic fibrosis (CF) aged 6 through 11 years, homozygous or heterozygous for F508del.

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	17 May 2018
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: 14
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Poland: 1
Worldwide total number of subjects	69
EEA total number of subjects	47

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	0

months)	
Children (2-11 years)	69
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 69 subjects were randomized, out of which 67 subjects received study drug and were included in subject disposition and baseline characteristics section.

Period 1

Period 1 title	Overall 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	Placebo

Arm description:

Subjects with genotype F/F received placebo matched to TEZ/IVA fixed dose combination (FDC) in the morning and placebo matched to IVA in the evening for 8 weeks.

Arm type	Blinding arm
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 in the morning.

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.

Arm title	TEZ/IVA

Arm description:

Subjects with genotype F/F received TEZ/IVA FDC in the morning and IVA in the evening for 8 weeks. Subjects with genotype F/RF received TEZ/IVA FDC and placebo matched to IVA in the morning and IVA in the evening for 8 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/IVA 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.

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 morning.

Arm title	Ivacaftor

Arm description:

Subjects with genotype F/RF received placebo matched to TEZ/IVA FDC in the morning and IVA in morning and evening for 8 weeks.

Arm type	Blinding arm
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	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 in the morning.

Number of subjects in period 1[1]	Placebo	TEZ/IVA	Ivacaftor
Started	10	54	3
Completed	10	53	3
Not completed	0	1	0
Other	-	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 69 subjects were randomized, out of which 67 subjects received study drug and were included in subject disposition and baseline characteristics section.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects with genotype F/F received placebo matched to TEZ/IVA fixed dose combination (FDC) in the morning and placebo matched to IVA in the evening for 8 weeks.	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects with genotype F/F received TEZ/IVA FDC in the morning and IVA in the evening for 8 weeks. Subjects with genotype F/RF received TEZ/IVA FDC and placebo matched to IVA in the morning and IVA in the evening for 8 weeks.	
Reporting group title	Ivacaftor
Reporting group description:	
Subjects with genotype F/RF received placebo matched to TEZ/IVA FDC in the morning and IVA in morning and evening for 8 weeks.	

Reporting group values	Placebo	TEZ/IVA	Ivacaftor
Number of subjects	10	54	3
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.0	8.5	9.0
standard deviation	± 1.7	± 1.7	± 1.7
Gender categorical Units: Subjects			
Female	6	29	2
Male	4	25	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	10	46	3
Unknown or Not Reported	0	7	0
Race 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	1	0
White	10	51	3
More than one race	0	0	0
Unknown or Not Reported	0	2	0
Lung Clearance Index 2.5 (LCI2.5)			
LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value.			
Units: Lung clearance index			
arithmetic mean	9.67	9.56	8.60

standard deviation	± 1.65	± 2.06	± 1.40

Reporting group values	Total		
Number of subjects	67		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	37		
Male	30		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	59		
Unknown or Not Reported	7		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	64		
More than one race	0		
Unknown or Not Reported	2		
Lung Clearance Index 2.5 (LCI2.5)			
LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value.			
Units: Lung clearance index arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects with genotype F/F received placebo matched to TEZ/IVA fixed dose combination (FDC) in the morning and placebo matched to IVA in the evening for 8 weeks.	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects with genotype F/F received TEZ/IVA FDC in the morning and IVA in the evening for 8 weeks. Subjects with genotype F/RF received TEZ/IVA FDC and placebo matched to IVA in the morning and IVA in the evening for 8 weeks.	
Reporting group title	Ivacaftor
Reporting group description:	
Subjects with genotype F/RF received placebo matched to TEZ/IVA FDC in the morning and IVA in morning and evening for 8 weeks.	

Primary: Absolute Change in Lung Clearance Index 2.5

End point title	Absolute Change in Lung Clearance Index 2.5[1][2]
End point description:	
LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. Full Analysis Set: all subjects who were randomized, received at least 1 dose of study drug and had an eligible genotype. As per the pre-specified analysis, efficacy was only planned to be assessed for TEZ/IVA group. Placebo or IVA groups were used for blinding purposes only and were not applicable for the purpose of primary efficacy analysis.	
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: The study was designed to perform within treatment group comparison. Because single group within treatment comparisons cannot be reported in the EudraCT database, no statistical analyses are 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 is applicable for only TEZ/IVA.

End point values	TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Lung clearance index				
least squares mean (standard error)	-0.51 (± 0.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Sweat Chloride At Week 8

End point title	Absolute Change in Sweat Chloride At Week 8[3]

End point description:

Sweat samples were collected using an approved collection device. FAS. As per the pre-specified analysis, efficacy was only planned to be assessed for TEZ/IVA group. Placebo or IVA groups were used for blinding purposes only and were not applicable for the purpose of secondary efficacy analysis.

End point type	Secondary

End point timeframe:

From baseline at 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 is applicable for only TEZ/IVA.

End point values	TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: millimole per liter (mmol/L)				
least squares mean (standard error)	-12.3 (± 1.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 8

End point title	Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score Through Week 8[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. As per the pre-specified analysis, efficacy was only planned to be assessed for TEZ/IVA group. Placebo or IVA groups were used for blinding purposes only and were not applicable for the purpose of secondary efficacy analysis.

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 is applicable for only TEZ/IVA.

End point values	TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: units on a scale				
least squares mean (standard error)	2.3 (± 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability as Assessed Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) up to Safety Follow-up Visit

End point title	Safety and Tolerability as Assessed Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) up to Safety Follow-up Visit

End point description:

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

End point type	Secondary

End point timeframe:

From first dose of study drug up to safety follow-up visit (up to Week 12)

End point values	Placebo	TEZ/IVA	Ivacaftor	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	54	3	
Units: subjects				
Subjects with AEs	8	41	2	
Subjects with SAEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up to safety follow-up visit (up to Week 12)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects with genotype F/F received placebo matched to TEZ/IVA FDC in the morning and placebo matched to IVA in the evening for 8 weeks.	
Reporting group title	TEZ/IVA
Reporting group description:	
Subjects with genotype F/F received TEZ/IVA FDC in the morning and IVA in the evening for 8 weeks. Subjects with genotype F/RF received TEZ/IVA FDC and placebo matched to IVA in the morning and IVA in the evening for 8 weeks.	
Reporting group title	Ivacaftor
Reporting group description:	
Subjects with genotype F/RF received placebo matched to TEZ/IVA FDC in the morning and IVA in morning and evening for 8 weeks.	

Serious adverse events	Placebo	TEZ/IVA	Ivacaftor
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo	TEZ/IVA	Ivacaftor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	31 / 54 (57.41%)	2 / 3 (66.67%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 54 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	8 / 54 (14.81%)	0 / 3 (0.00%)
occurrences (all)	1	11	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	4 / 54 (7.41%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	3 / 54 (5.56%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 10 (10.00%)	9 / 54 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	10	0
Sputum increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	3 / 54 (5.56%)	1 / 3 (33.33%)
occurrences (all)	0	4	1
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	7 / 54 (12.96%)	0 / 3 (0.00%)
occurrences (all)	1	9	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	3 / 54 (5.56%)	0 / 3 (0.00%)
occurrences (all)	0	3	0

Throat irritation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Blister			
subjects affected / exposed	0 / 10 (0.00%)	0 / 54 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 10 (20.00%)	3 / 54 (5.56%)	0 / 3 (0.00%)
occurrences (all)	4	3	0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	4 / 54 (7.41%)	0 / 3 (0.00%)
occurrences (all)	0	5	0
Bacterial disease carrier			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	5 / 54 (9.26%)	0 / 3 (0.00%)
occurrences (all)	1	5	0
Otitis media			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 54 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Impetigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 54 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 54 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 54 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

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