Clinical trial results:
A Phase 3, Randomized, Double-Blind, Ivacaftor-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation and a Second CFTR Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor Responsive.

Summary

EudraCT number	2014-004838-25
Trial protocol	IT IE BE AT DE
Global end of trial date	19 September 2017

Results information

Result version number	v1 (current)
This version publication date	20 May 2018
First version publication date	20 May 2018

Trial information

Trial identification

Sponsor protocol code	VX14-661-109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02412111
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 02210-1862
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 6173416777, medical_info@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, 1 6173416777, medical_info@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	06 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 September 2017
Global end of trial reached?	Yes
Global end of trial date	19 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-661 in combination with Ivacaftor in subjects with cystic fibrosis (CF) who were heterozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene and a second CFTR allele with a gating defect that was clinically demonstrated to be Ivacaftor responsive

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 2015
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 Kingdom: 21
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Canada: 7
Worldwide total number of subjects	156
EEA total number of subjects	57

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)	20
Adults (18-64 years)	135
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of 2 periods: an Ivacaftor Run-in Period and an Active Comparator Treatment Period. Subjects were randomized in a ratio of 1:1 to receive either VX-661/ivacaftor combination therapy or ivacaftor monotherapy for 8 weeks during the Active Comparator Treatment Period after completion of 4 weeks Ivacaftor Run-in Period.

Period 1

Period 1 title	Ivacaftor Run-in Period (4 weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ivacaftor (Run-in period)

Arm description:

Ivacaftor every 12 hours for 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor every 12 hours for 4 weeks.

Number of subjects in period 1	Ivacaftor (Run-in period)
Started	156
Completed	153
Not completed	3
Did not meet eligibility criteria	1
Subject refused further dosing	2

Period 2

Period 2 title	Active Comparator Period (8 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	VX-661 + Ivacaftor

Arm description:

VX-661 and ivacaftor fixed-dose combination once daily in morning and ivacaftor once daily in evening for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	VX-661/Ivacaftor Fixed Dose Combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

VX-661 and ivacaftor fixed-dose combination once daily in morning for 8 weeks.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor once daily in evening for 8 weeks.

Arm title	Ivacaftor monotherapy

Arm description:

Ivacaftor every 12 hours as monotherapy for 8 weeks.

Arm type	Active comparator
Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor every 12 hours as monotherapy for 8 weeks.

Number of subjects in period 2[1]	VX-661 + Ivacaftor	Ivacaftor monotherapy
Started	76	75
Full analysis set	76	74
Completed	75	69
Not completed	1	6
Adverse event	-	2
Unspecified	-	2
Other non-compliance	1	-
Lost to follow-up	-	1
Subject refused further dosing	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Two subjects who completed the Run-in period did not enter the active comparator period.

Baseline characteristics

Reporting groups	
Reporting group title	Ivacaftor (Run-in period)
Reporting group description: Ivacaftor every 12 hours for 4 weeks.	

Reporting group values	Ivacaftor (Run-in period)	Total	
Number of subjects	156	156	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32.1		
standard deviation	± 12.1	-	
Gender categorical Units: Subjects			
Female	68	68	
Male	88	88	

End points

End points reporting groups

Reporting group title	Ivacaftor (Run-in period)
Reporting group description:	
Ivacaftor every 12 hours for 4 weeks.	
Reporting group title	VX-661 + Ivacaftor
Reporting group description:	
VX-661 and ivacaftor fixed-dose combination once daily in morning and ivacaftor once daily in evening for 8 weeks.	
Reporting group title	Ivacaftor monotherapy
Reporting group description:	
Ivacaftor every 12 hours as monotherapy for 8 weeks.	

Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 8

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 8

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Full Analysis Set was defined as all randomized subjects who have received at least 1 dose of blinded study drug during the active comparator treatment period. Here "Number of subjects analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Primary
End point timeframe:	
Baseline, Through Week 8	

End point values	VX-661 + Ivacaftor	Ivacaftor monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	72		
Units: Percent predicted of FEV1				
least squares mean (standard error)	0.5 (± 0.4)	0.2 (± 0.4)		

Statistical analyses

Statistical analysis title	Absolute Change From Baseline In ppFEV1
Comparison groups	VX-661 + Ivacaftor v Ivacaftor monotherapy

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5846
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Square (LS) mean difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 16	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Ivacaftor (Run-in period)
Reporting group description: Ivacaftor every 12 hours for 4 weeks.	
Reporting group title	VX-661 + Ivacaftor (Active comparator period)
Reporting group description: VX-661 and ivacaftor fixed-dose combination once daily in morning and ivacaftor once daily in evening for 8 weeks.	
Reporting group title	Ivacaftor monotherapy (Active comparator period)
Reporting group description: Ivacaftor every 12 hours as monotherapy for 8 weeks.	

Serious adverse events	Ivacaftor (Run-in period)	VX-661 + Ivacaftor (Active comparator period)	Ivacaftor monotherapy (Active comparator period)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 156 (1.28%)	4 / 76 (5.26%)	7 / 75 (9.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Human rhinovirus test positive			
subjects affected / exposed	1 / 156 (0.64%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Idiopathic intracranial hypertension			
subjects affected / exposed	0 / 156 (0.00%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			

subjects affected / exposed	1 / 156 (0.64%)	0 / 76 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	0 / 156 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 156 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 156 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 156 (0.00%)	0 / 76 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 156 (0.64%)	2 / 76 (2.63%)	5 / 75 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 156 (0.00%)	1 / 76 (1.32%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ivacaftor (Run-in period)	VX-661 + Ivacaftor (Active comparator period)	Ivacaftor monotherapy (Active comparator period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 156 (41.67%)	76 / 76 (100.00%)	53 / 75 (70.67%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 156 (1.28%)	4 / 76 (5.26%)	0 / 75 (0.00%)
occurrences (all)	2	4	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 156 (2.56%)	5 / 76 (6.58%)	2 / 75 (2.67%)
occurrences (all)	4	5	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 156 (1.92%)	0 / 76 (0.00%)	4 / 75 (5.33%)
occurrences (all)	3	0	4
Diarrhoea			
subjects affected / exposed	2 / 156 (1.28%)	4 / 76 (5.26%)	1 / 75 (1.33%)
occurrences (all)	2	4	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 156 (7.69%)	12 / 76 (15.79%)	12 / 75 (16.00%)
occurrences (all)	12	13	13
Sputum increased			
subjects affected / exposed	8 / 156 (5.13%)	4 / 76 (5.26%)	7 / 75 (9.33%)
occurrences (all)	8	5	8
Haemoptysis			
subjects affected / exposed	3 / 156 (1.92%)	3 / 76 (3.95%)	4 / 75 (5.33%)
occurrences (all)	3	3	5
Infections and infestations			

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 156 (1.28%)	6 / 76 (7.89%)	4 / 75 (5.33%)
occurrences (all)	2	6	5
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 156 (0.64%)	4 / 76 (5.26%)	6 / 75 (8.00%)
occurrences (all)	1	4	6
Headache			
subjects affected / exposed	10 / 156 (6.41%)	6 / 76 (7.89%)	4 / 75 (5.33%)
occurrences (all)	10	6	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2015	- Specified criteria for sweat chloride assessment at Screening Visit - Added an ophthalmologic examination - Removed some of the study endpoints
08 October 2015	- Included potential to extend Ivacaftor Run-in Period - Added a window to the Visit during the Ivacaftor Run-in Period
18 April 2017	- Reduced the planned number of subjects enrolled

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported