

**Clinical trial results:****A Phase 3, Randomized, Double-blind, Placebo-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 With a Second CFTR Mutation That Is Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (F508del/NR)****Summary**

EudraCT number	2014-004787-37
Trial protocol	AT DE ES
Global end of trial date	12 August 2016

**Results information**

Result version number	v1 (current)
This version publication date	01 March 2017
First version publication date	01 March 2017

**Trial information****Trial identification**

Sponsor protocol code	VX14-661-107
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02516410
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, 1 617-341-6777, 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?	No

Notes:

### Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 October 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 August 2016
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 through Week 12 in subjects with cystic fibrosis (CF) who are heterozygous for the F508del- CF transmembrane conductance regulator (CFTR) gene and with a second CFTR mutation that is not likely to respond to VX-661 and/or ivacaftor therapy (F508del/not responsive [NR]).

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	15 August 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 States: 89
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	168
EEA total number of subjects	34

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)	37
Adults (18-64 years)	131
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted across 38 sites in 7 countries.

### Pre-assignment

Screening details:

A total of 168 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
<b>Arm title</b>	Placebo

Arm description:

Placebo matched to VX-661 plus Ivacaftor (IVA, VX-770) fixed dose combination (FDC) tablet administered orally in the morning and placebo matched to IVA film-coated tablet administered orally in the evening up to Week 12.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-661 plus IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to VX-661 plus IVA supplied as FDC tablet administered orally in the morning up to Week 12.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to IVA film-coated tablet administered orally in the evening up to Week 12.

<b>Arm title</b>	VX-661/IVA
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Arm description:

VX-661 100 milligram (mg) plus IVA 150 mg FDC tablet administered orally in the morning and IVA 150 mg film-coated tablet administered orally in the evening up to Week 12.

Arm type	Experimental
Investigational medicinal product name	VX-661 Plus IVA Fixed Dose Combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

VX-661 100 mg plus IVA 150 mg supplied as FDC tablet administered orally in the morning up to Week 12.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor 150 mg film-coated tablet administered orally in the evening up to Week 12.

<b>Number of subjects in period 1</b>	Placebo	VX-661/IVA
Started	85	83
Completed	85	81
Not completed	0	2
Consent withdrawn by subject	-	1
Adverse event	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo matched to VX-661 plus Ivacaftor (IVA, VX-770) fixed dose combination (FDC) tablet administered orally in the morning and placebo matched to IVA film-coated tablet administered orally in the evening up to Week 12.

Reporting group title	VX-661/IVA
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Reporting group description:

VX-661 100 milligram (mg) plus IVA 150 mg FDC tablet administered orally in the morning and IVA 150 mg film-coated tablet administered orally in the evening up to Week 12.

Reporting group values	Placebo	VX-661/IVA	Total
Number of subjects	85	83	168
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	26	26.2	
standard deviation	± 8.8	± 9.6	-
Gender categorical Units: Subjects			
Female	42	39	81
Male	43	44	87

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to VX-661 plus Ivacaftor (IVA, VX-770) fixed dose combination (FDC) tablet administered orally in the morning and placebo matched to IVA film-coated tablet administered orally in the evening up to Week 12.	
Reporting group title	VX-661/IVA
Reporting group description: VX-661 100 milligram (mg) plus IVA 150 mg FDC tablet administered orally in the morning and IVA 150 mg film-coated tablet administered orally in the evening up to Week 12.	

### Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 12

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 12
End point description: FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Hankinson and Wang standards were used to calculate percent predicted FEV1 (for age, gender, and height). The Hankinson standard was used for male subjects 18 years and older and female subjects 16 years and older. The Wang standard was used for male subjects aged 12 to 17 years and for female subjects aged 12 to 15 years. Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug. Here 'Number of subjects analysed' signifies those subjects who were evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline through Week 12	

End point values	Placebo	VX-661/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	82		
Units: percent predicted of FEV1				
least squares mean (standard error)	-0.1 ( $\pm$ 0.6)	1 ( $\pm$ 0.6)		

### Statistical analyses

Statistical analysis title	Change in percent predicted FEV1 Through Week 12
Comparison groups	Placebo v VX-661/IVA
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1176
Method	Mixed-effect repeated measure (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	1.2

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Confidence interval

level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.6

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 16

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo matched to VX-661 plus IVA FDC tablet administered orally in the morning and placebo matched to IVA film-coated tablet administered orally in the evening up to Week 12.

Reporting group title	VX-661/IVA
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Reporting group description:

VX-661 100 mg plus IVA 150 mg FDC tablet administered orally in the morning and IVA 150 mg film-coated tablet administered orally in the evening up to Week 12.

<b>Serious adverse events</b>	Placebo	VX-661/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 85 (16.47%)	11 / 83 (13.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 85 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 85 (0.00%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 85 (1.18%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (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	12 / 85 (14.12%)	6 / 83 (7.23%)	
occurrences causally related to treatment / all	2 / 12	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 85 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 83 (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 %

<b>Non-serious adverse events</b>	Placebo	VX-661/IVA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 85 (74.12%)	62 / 83 (74.70%)	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 7	5 / 83 (6.02%) 5	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	4 / 85 (4.71%) 4  5 / 85 (5.88%) 6	10 / 83 (12.05%) 11  5 / 83 (6.02%) 5	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	6 / 85 (7.06%) 7	6 / 83 (7.23%) 6	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Haemoptysis subjects affected / exposed occurrences (all)  Nasal congestion subjects affected / exposed occurrences (all)  Sputum increased subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	27 / 85 (31.76%) 31  6 / 85 (7.06%) 7  8 / 85 (9.41%) 8  12 / 85 (14.12%) 15  7 / 85 (8.24%) 7  6 / 85 (7.06%) 6	19 / 83 (22.89%) 20  8 / 83 (9.64%) 12  7 / 83 (8.43%) 9  7 / 83 (8.43%) 7  5 / 83 (6.02%) 5  5 / 83 (6.02%) 5	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	15 / 85 (17.65%)	17 / 83 (20.48%)	
occurrences (all)	19	21	
Nasopharyngitis			
subjects affected / exposed	5 / 85 (5.88%)	2 / 83 (2.41%)	
occurrences (all)	5	2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2015	- Increased the number of planned subjects to account for an interim analysis for futility. - Added washout requirements for subjects who have previously used a commercially available CFTR modulator. - For < 18 years of age, added post-dose spirometry assessments and added ophthalmologic examination at the Early Treatment Termination (ETT) Visit or Safety Follow-up Visit.
15 April 2016	- Added that ophthalmologic examinations were not required for subjects with documentation of bilateral lens removal. - Specified that the sweat chloride test at screening is optional if the subject's medical record is used to establish eligibility. - Allowed CFTR genotype information from a previous CFTR genotype laboratory report to be used in cases where results from genotype assessment at screening are not available before randomization. - Removed Pittsburgh Sleep Quality Index (PSQI) assessment at Day 15. - Revised the description of the timing of the spirometry assessment relative to bronchodilator use. - Added a window of $\pm$ 15 minutes around the nominal times for all postdose ECG assessments.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported