

**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, Homozygous for the F508del CFTR Mutation****Summary**

EudraCT number	2014-004837-13
Trial protocol	IE SE GB DK IT NL DE ES
Global end of trial date	20 January 2017

**Results information**

Result version number	v1 (current)
This version publication date	25 August 2017
First version publication date	25 August 2017

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

Sponsor protocol code	VX14-661-106
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02347657
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States, 022101862
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)	EMA-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	21 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2017
Global end of trial reached?	Yes
Global end of trial date	20 January 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 (IVA, VX-770) through Week 24 in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene.

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	30 January 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	Netherlands: 50
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Ireland: 19
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	United States: 102
Country: Number of subjects enrolled	Switzerland: 26
Country: Number of subjects enrolled	Canada: 25
Worldwide total number of subjects	510
EEA total number of subjects	357

Notes:

### Subjects enrolled per age group

In utero	0
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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)	118
Adults (18-64 years)	392
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted across 91 sites in 12 countries.

### Pre-assignment

Screening details:

A total of 510 subjects were randomized and 509 subjects were 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 IVA in the morning and placebo matched to IVA in the evening up to Week 24.

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 fixed dose combination (FDC) in the morning up to Week 24.

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 in the evening up to Week 24.

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

VX-661 plus IVA in the morning and IVA in the evening up to Week 24.

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

Dosage and administration details:

VX-661 plus IVA FDC in the morning up to Week 24.

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:

IVA in the evening up to Week 24.

<b>Number of subjects in period 1</b>	Placebo	VX-661/IVA
Started	259	251
Treated	258	251
Completed	241	236
Not completed	18	15
Consent withdrawn by subject	6	7
Physician decision	-	1
Adverse event	8	4
Randomised but not treated	1	-
Unspecified	3	3

## Baseline characteristics

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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo matched to VX-661 plus IVA in the morning and placebo matched to IVA in the evening up to Week 24.

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

VX-661 plus IVA in the morning and IVA in the evening up to Week 24.

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Reporting group values	Placebo	VX-661/IVA	Total
Number of subjects	259	251	510
Age categorical Units: Subjects			
<18 Years	60	58	118
>=18 Years	199	193	392
Gender categorical Units: Subjects			
Female	126	121	247
Male	133	130	263

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo matched to VX-661 plus IVA in the morning and placebo matched to IVA in the evening up to Week 24.	
Reporting group title	VX-661/IVA
Reporting group description: VX-661 plus IVA in the morning and IVA in the evening up to Week 24.	

### Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) Through Week 24
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 carry the intended CFTR allele mutation and have 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 24	

End point values	Placebo	VX-661/IVA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	245		
Units: percent predicted of FEV1				
least squares mean (standard error)	-0.6 (± 0.3)	3.4 (± 0.3)		

### Statistical analyses

Statistical analysis title	Change in percent predicted FEV1 Through Week 24
Comparison groups	Placebo v VX-661/IVA
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	4

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	4.8



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 28

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 in the morning and placebo matched to IVA in the evening up to Week 24.

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

VX-661 plus IVA in the morning and IVA in the evening up to Week 24.

Serious adverse events	Placebo	VX-661/IVA	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 258 (18.22%)	31 / 251 (12.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 258 (0.39%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose abnormal			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			

subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Benign intracranial hypertension			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (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			
Chest discomfort			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac disease			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 258 (0.78%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	3 / 258 (1.16%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal cyst			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 258 (0.78%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			

subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	32 / 258 (12.40%)	23 / 251 (9.16%)	
occurrences causally related to treatment / all	0 / 38	1 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 258 (0.39%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 258 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acarodermatitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			

subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 258 (0.39%)	0 / 251 (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	243 / 258 (94.19%)	227 / 251 (90.44%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 258 (5.04%)	8 / 251 (3.19%)	
occurrences (all)	13	8	
Bacterial test positive			
subjects affected / exposed	16 / 258 (6.20%)	8 / 251 (3.19%)	
occurrences (all)	19	11	
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 258 (13.95%)	44 / 251 (17.53%)	
occurrences (all)	59	57	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	32 / 258 (12.40%)	28 / 251 (11.16%)	
occurrences (all)	38	39	
Fatigue			
subjects affected / exposed	30 / 258 (11.63%)	16 / 251 (6.37%)	
occurrences (all)	33	19	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	22 / 258 (8.53%)	23 / 251 (9.16%)	
occurrences (all)	29	28	
Nausea			
subjects affected / exposed	18 / 258 (6.98%)	23 / 251 (9.16%)	
occurrences (all)	21	26	
Diarrhoea			
subjects affected / exposed	23 / 258 (8.91%)	17 / 251 (6.77%)	
occurrences (all)	32	21	
Vomiting			
subjects affected / exposed	15 / 258 (5.81%)	13 / 251 (5.18%)	
occurrences (all)	17	13	
Abdominal pain upper			
subjects affected / exposed	17 / 258 (6.59%)	10 / 251 (3.98%)	
occurrences (all)	21	12	
Constipation			
subjects affected / exposed	14 / 258 (5.43%)	7 / 251 (2.79%)	
occurrences (all)	14	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	83 / 258 (32.17%)	66 / 251 (26.29%)	
occurrences (all)	114	84	
Sputum increased			
subjects affected / exposed	42 / 258 (16.28%)	36 / 251 (14.34%)	
occurrences (all)	48	41	
Haemoptysis			
subjects affected / exposed	33 / 258 (12.79%)	24 / 251 (9.56%)	
occurrences (all)	43	30	
Oropharyngeal pain			
subjects affected / exposed	29 / 258 (11.24%)	22 / 251 (8.76%)	
occurrences (all)	36	23	
Dyspnoea			
subjects affected / exposed	18 / 258 (6.98%)	16 / 251 (6.37%)	
occurrences (all)	24	18	
Rhinorrhoea			

subjects affected / exposed occurrences (all)	16 / 258 (6.20%) 17	8 / 251 (3.19%) 8	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	13 / 258 (5.04%) 16	4 / 251 (1.59%) 4	
Infections and infestations Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)  Rhinitis subjects affected / exposed occurrences (all)	75 / 258 (29.07%) 105  39 / 258 (15.12%) 55  14 / 258 (5.43%) 15	57 / 251 (22.71%) 73  42 / 251 (16.73%) 54  10 / 251 (3.98%) 10	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2015	- Addition of Cystic Fibrosis Questionnaire-Revised (CFQ-R) assessment at selected Visits.
08 June 2015	- Addition of post-dose spirometry and ophthalmologic examinations.
06 May 2016	- Revised exclusion criterion to exclude subjects who received lumacaftor/ivacaftor commercially.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported