Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and 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 Allele With a CFTR Mutation Predicted to Have Residual Function

Summary

EudraCT number	2014-004788-18
Trial protocol	IT DE NL GB BE
Global end of trial date	16 February 2017

Results information

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

Trial information

Trial identification

Sponsor protocol code	VX14-661-108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02392234
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)	EMEA-001640-PIP01-04
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	14 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2017
Global end of trial reached?	Yes
Global end of trial date	16 February 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 and ivacaftor monotherapy through 8 weeks of treatment in subjects with cystic fibrosis (CF) who are heterozygous for the F508del mutation on the CF transmembrane conductance regulator (CFTR) gene and a second allele with a CFTR mutation predicted to have residual function.

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	27 March 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: 13
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	United States: 115
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Israel: 7
Worldwide total number of subjects	248
EEA total number of subjects	109

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)	34
Adults (18-64 years)	212
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 81 sites in 10 countries.

Pre-assignment

Screening details:

A total of 248 subjects were randomized to 1 of 6 treatment sequences, each of which included 2 treatment periods and 2 of 3 potential treatments (placebo, VX-661/IVA, IVA).

Period 1

Period 1 title	Treatment Period 1 (8 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	First VX-661/IVA, Then IVA - Treatment 1: VX-661/IVA

Arm description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

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

Dosage and administration details:

VX-661 plus IVA Fixed Dose Combination (FDC) in the morning for 8 weeks.

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 morning for 8 weeks.

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 for 8 weeks.

Arm title	First VX-661/IVA, Then Placebo - Treatment 1: VX-661/IVA

Arm description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo

matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	VX-661 Plus IVA Combination
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 for 8 weeks.

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 morning for 8 weeks.

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 for 8 weeks.

Arm title	First IVA, Then Placebo - Treatment 1: IVA

Arm description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

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 morning and evening for 8 weeks.

Arm title	First IVA, Then VX-661/IVA - Treatment 1: IVA

Arm description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental

Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

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 morning and evening for 8 weeks.

Arm title	First Placebo, Then VX-661/IVA - Treatment 1: Placebo

Arm description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to IVA in the morning and evening for 8 weeks.

Arm title	First Placebo, Then IVA - Treatment 1: Placebo

Arm description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet

Routes of administration	Oral use

Dosage and administration details:

Placebo matched to IVA in the morning and evening for 8 weeks.

Number of subjects in period 1	First VX-661/IVA, Then IVA - Treatment 1: VX-661/IVA	First VX-661/IVA, Then Placebo - Treatment 1: VX-661/IVA	First IVA, Then Placebo - Treatment 1: IVA
Started	41	43	40
Treated	41	43	39
Completed	38	43	38
Not completed	3	0	2
Consent withdrawn by subject	-	-	-
Randomized but not treated	-	-	1
Non compliance of study drug	-	-	-
Adverse event	1	-	1
Unspecified	1	-	-
Lost to follow-up	-	-	-
Pregnancy	1	-	-

Number of subjects in period 1	First IVA, Then VX-661/IVA - Treatment 1: IVA	First Placebo, Then VX-661/IVA - Treatment 1: Placebo	First Placebo, Then IVA - Treatment 1: Placebo
Started	42	41	41
Treated	42	40	41
Completed	41	37	38
Not completed	1	4	3
Consent withdrawn by subject	-	2	-
Randomized but not treated	-	1	-
Non compliance of study drug	-	-	1
Adverse event	-	1	1
Unspecified	-	-	-
Lost to follow-up	-	-	1
Pregnancy	1	-	-

Period 2

Period 2 title	Treatment Period 2 (8 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	First VX-661/IVA, Then IVA - Treatment 2: IVA

Arm description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

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 morning and evening for 8 weeks.

Arm title	First VX-661/IVA, Then Placebo - Treatment 2: Placebo

Arm description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to IVA in the morning and evening for 8 weeks.

Arm title	First IVA, Then Placebo - Treatment 2: Placebo

Arm description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to IVA in the morning and evening for 8 weeks.

Arm title	First IVA, Then VX-661/IVA - Treatment 2: VX-661/IVA

Arm description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	VX-661 Plus IVA Combination
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 for 8 weeks.

Investigational medicinal product name	Placebo (matched to IVA)
Investigational medicinal product code	VX-770
Other name	Kalydeco
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to IVA in the morning for 8 weeks.

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 for 8 weeks.

Arm title	First Placebo, Then VX-661/IVA - Treatment 2: VX-661/IVA

Arm description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	VX-661 Plus IVA Combination
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 for 8 weeks.

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 morning for 8 weeks.

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 for 8 weeks.

Arm title	First Placebo, Then IVA - Treatment 2: IVA

Arm description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)
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 FDC in the morning for 8 weeks.

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 morning and evening for 8 weeks.

Number of subjects in period 2	First VX-661/IVA, Then IVA - Treatment 2: IVA	First VX-661/IVA, Then Placebo - Treatment 2: Placebo	First IVA, Then Placebo - Treatment 2: Placebo
Started	38	43	38
Completed	37	43	38
Not completed	1	0	0
Adverse event	1	-	-

Number of subjects in period 2	First IVA, Then VX-661/IVA - Treatment 2: VX-661/IVA	First Placebo, Then VX-661/IVA - Treatment 2: VX-661/IVA	First Placebo, Then IVA - Treatment 2: IVA
Started	41	37	38
Completed	41	37	38
Not completed	0	0	0
Adverse event	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	First VX-661/IVA, Then IVA - Treatment 1: VX-661/IVA

Reporting group description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First VX-661/IVA, Then Placebo - Treatment 1: VX-661/IVA

Reporting group description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First IVA, Then Placebo - Treatment 1: IVA

Reporting group description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First IVA, Then VX-661/IVA - Treatment 1: IVA

Reporting group description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First Placebo, Then VX-661/IVA - Treatment 1: Placebo

Reporting group description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First Placebo, Then IVA - Treatment 1: Placebo

Reporting group description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group values	First VX-661/IVA, Then IVA - Treatment 1: VX-661/IVA	First VX-661/IVA, Then Placebo - Treatment 1: VX-661/IVA	First IVA, Then Placebo - Treatment 1: IVA
Number of subjects	41	43	40
Age categorical Units: Subjects			
<18 Years	5	6	7
>=18 Years	36	37	33
Gender categorical Units: Subjects			
Female	23	25	19
Male	18	18	21

Reporting group values	First IVA, Then VX-661/IVA - Treatment	First Placebo, Then VX-661/IVA -	First Placebo, Then IVA - Treatment 1:

	1: IVA	Treatment 1: Placebo	Placebo
Number of subjects	42	41	41
Age categorical Units: Subjects			
<18 Years	5	5	6
>=18 Years	37	36	35
Gender categorical Units: Subjects			
Female	21	23	23
Male	21	18	18

Reporting group values	Total		
Number of subjects	248		
Age categorical Units: Subjects			
<18 Years	34		
>=18 Years	214		
Gender categorical Units: Subjects			
Female	134		
Male	114		

End points

End points reporting groups

Reporting group title	First VX-661/IVA, Then IVA - Treatment 1: VX-661/IVA

Reporting group description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First VX-661/IVA, Then Placebo - Treatment 1: VX-661/IVA

Reporting group description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First IVA, Then Placebo - Treatment 1: IVA

Reporting group description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First IVA, Then VX-661/IVA - Treatment 1: IVA

Reporting group description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First Placebo, Then VX-661/IVA - Treatment 1: Placebo

Reporting group description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First Placebo, Then IVA - Treatment 1: Placebo

Reporting group description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First VX-661/IVA, Then IVA - Treatment 2: IVA

Reporting group description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First VX-661/IVA, Then Placebo - Treatment 2: Placebo

Reporting group description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First IVA, Then Placebo - Treatment 2: Placebo

Reporting group description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First IVA, Then VX-661/IVA - Treatment 2: VX-661/IVA

Reporting group description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First Placebo, Then VX-661/IVA - Treatment 2: VX-661/IVA

Reporting group description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Reporting group title	First Placebo, Then IVA - Treatment 2: IVA

Reporting group description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in treatment period 2. Each treatment period was separated by a minimum 8 weeks of washout period.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in either treatment period 1 or 2.

Subject analysis set title	Ivacaftor
Subject analysis set type	Full analysis

Subject analysis set description:

IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in either treatment period 1 or 2.

Subject analysis set title	VX-661/IVA
Subject analysis set type	Full analysis

Subject analysis set description:

VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in either treatment period 1 or 2.

Primary: Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Average of Week 4 and Week 8

End point title	Absolute Change From Baseline in Percent Predicted Forced Expiratory Volume in 1 Second (FEV1) at Average of Week 4 and Week 8

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. The average absolute change from baseline in percent predicted FEV1 was derived as: (Average of Week 4 and Week 8 value) minus Baseline value. 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, Week 4 and Week 8 of each treatment period

End point values	Placebo	Ivacaftor	VX-661/IVA	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	160	156	159	
Units: percent predicted of FEV1				
least squares mean (standard error)	-0.3 (± 0.5)	4.4 (± 0.5)	6.5 (± 0.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

For 'number of subjects included in the analysis' field: total number of subjects analysed were 160 instead of 316 because this study is a cross-over design and same subjects may have received both the interventions.

Comparison groups	Placebo v Ivacaftor
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear Mixed Effects Model
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	5.8

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

For 'number of subjects included in the analysis' field: total number of subjects analysed were 160 instead of 319 because this study is a cross-over design and same subjects may have received both the interventions.

Comparison groups	Placebo v VX-661/IVA
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Linear Mixed Effects Model
Parameter estimate	LS Mean Difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	7.8

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA in the evening for 8 weeks in either treatment period 1 or 2.	
Reporting group title	Ivacaftor
Reporting group description:	
IVA and placebo matched to VX-661 plus IVA combination in the morning, IVA in the evening for 8 weeks in either treatment period 1 or 2.	
Reporting group title	VX-661/IVA
Reporting group description:	
VX-661 plus IVA combination and placebo matched to IVA in the morning, IVA in the evening for 8 weeks in either treatment period 1 or 2.	

Serious adverse events	Placebo	Ivacaftor	VX-661/IVA
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 162 (8.64%)	10 / 157 (6.37%)	8 / 162 (4.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 162 (0.00%)	2 / 157 (1.27%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary function test decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 157 (0.00%)	0 / 162 (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
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	0 / 162 (0.00%)	0 / 157 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 162 (0.00%)	0 / 157 (0.00%)	1 / 162 (0.62%)
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			
Abdominal pain			
subjects affected / exposed	2 / 162 (1.23%)	0 / 157 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 157 (0.64%)	0 / 162 (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
Pancreatitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 157 (0.64%)	0 / 162 (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
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 162 (0.62%)	0 / 157 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 162 (0.62%)	0 / 157 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			

subjects affected / exposed	2 / 162 (1.23%)	1 / 157 (0.64%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 157 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 162 (0.62%)	0 / 157 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urethral stenosis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 157 (0.00%)	0 / 162 (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
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	8 / 162 (4.94%)	6 / 157 (3.82%)	4 / 162 (2.47%)
occurrences causally related to treatment / all	1 / 8	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 162 (0.00%)	0 / 157 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 162 (1.23%)	0 / 157 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	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	Placebo	Ivacaftor	VX-661/IVA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 162 (77.16%)	114 / 157 (72.61%)	117 / 162 (72.22%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 162 (8.02%)	11 / 157 (7.01%)	18 / 162 (11.11%)
occurrences (all)	20	14	25
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 162 (9.88%)	7 / 157 (4.46%)	12 / 162 (7.41%)
occurrences (all)	17	7	12
Pyrexia			
subjects affected / exposed	12 / 162 (7.41%)	2 / 157 (1.27%)	8 / 162 (4.94%)
occurrences (all)	12	2	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 162 (6.17%)	5 / 157 (3.18%)	13 / 162 (8.02%)
occurrences (all)	10	6	13
Nausea			
subjects affected / exposed	10 / 162 (6.17%)	3 / 157 (1.91%)	9 / 162 (5.56%)
occurrences (all)	10	4	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 162 (18.52%)	17 / 157 (10.83%)	23 / 162 (14.20%)
occurrences (all)	36	18	27
Sputum increased			
subjects affected / exposed	11 / 162 (6.79%)	12 / 157 (7.64%)	14 / 162 (8.64%)
occurrences (all)	13	12	16
Haemoptysis			
subjects affected / exposed	12 / 162 (7.41%)	17 / 157 (10.83%)	12 / 162 (7.41%)
occurrences (all)	15	20	18
Dyspnoea			
subjects affected / exposed	11 / 162 (6.79%)	3 / 157 (1.91%)	9 / 162 (5.56%)
occurrences (all)	11	3	11
Oropharyngeal pain			

subjects affected / exposed	9 / 162 (5.56%)	7 / 157 (4.46%)	9 / 162 (5.56%)
occurrences (all)	9	7	9
Nasal congestion			
subjects affected / exposed	9 / 162 (5.56%)	3 / 157 (1.91%)	6 / 162 (3.70%)
occurrences (all)	9	3	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 162 (3.09%)	6 / 157 (3.82%)	13 / 162 (8.02%)
occurrences (all)	6	7	14
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	25 / 162 (15.43%)	14 / 157 (8.92%)	19 / 162 (11.73%)
occurrences (all)	25	14	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2015	- Added additional assessments; - Allowed Screening Period to be extended; - Revised restricted medication list; - Added washout requirements for subjects who previously used commercially available CFTR modulator; - Added details to determine eligible CTFR mutations; - Revised the list of eligible mutations.
10 June 2016	- Clarified the timing of the Washout Period; - Clarified the inclusion criteria with sweat chloride; - Clarified screening assessments; - Revised the description of assessments; - Revised the testing strategy; - Clarified baseline sweat chloride values.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported