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)	-
Natas	

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

Results analysis stage

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

Subjects enfonce 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	n (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.

Α

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.

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.	
weeks in treatment period 1 followed by matched to IVA in the morning, placebo	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period
weeks in treatment period 1 followed by matched to IVA in the morning, placebo	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period.
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination)
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details:	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks.
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco Film-coated tablet
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco Film-coated tablet Oral use
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco Film-coated tablet Oral use
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration Dosage and administration Dosage and administration Marmatile	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco Film-coated tablet Oral use
 weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product code Other name Pharmaceutical forms Routes of administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: IVA in the morning and evening for 8 we Arm title Arm description: IVA and placebo matched to VX-661 plu weeks in treatment period 1 followed by the morning, IVA in the evening for 8 we separated by a minimum 8 weeks of wa 	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco Film-coated tablet Oral use eeks. First IVA, Then VX-661/IVA - Treatment 1: IVA
weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Placebo matched to VX-661 plus IVA FD Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration Dosage and administration Marmaceutical forms Routes of administration Dosage and administration Marm title Arm description: IVA and placebo matched to VX-661 plu weeks in treatment period 1 followed by the morning, IVA in the evening for 8 wo	placebo matched to VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period by a minimum 8 weeks of washout period. Experimental Placebo (matched to VX-661 Plus IVA Combination) Film-coated tablet Oral use C in the morning for 8 weeks. Ivacaftor VX-770 Kalydeco Film-coated tablet Oral use eeks. First IVA, Then VX-661/IVA - Treatment 1: IVA

Investigational medicinal product ande 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 film for 8 weeks. Investigational medicinal product name Ivx-770 Other name Kalydeco Pharmaccutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: IVA in the morning for 8 weeks. Arm title First Placebo, Then VX-661/IVA - Treatment 1: Placebo Arm type Placebo Investigational medicinal product name Placebo			
Other name Film-coated tablet Pharmaccutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebornatched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product name Ivacaftor Investigational medicinal product name Ivacaftor 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 IVA of 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 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 name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to IVA in the evening for 8 weeks. Investigational medicinal product name	Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)	
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 Ivacator 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 evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period as separated by a minimum 8 weeks of washout period. Investigational medicinal product code Investigational medicinal product code Other name Film-coated tablet Posage and administration Oral use Dosage and administration	Investigational medicinal product code		
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 code VX-770 Other name Kalydeco Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: VX-70 VIA in the morning and evening for 8 weeks. Investigational medicinal product code 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 on 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 (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Queeto (matched to VX-661 Plus IVA combination) Investigational medicinal product code Placebo (matched to VX-661 Plus IVA combination) Investigational medicinal product code Queeto (matched to IVA) Investigational medicinal product code VX-770 Other name <td< td=""><td>Other name</td><td></td></td<>	Other name		
Dosage and administration details: Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. 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 evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA Investigational medicinal product name Placebo Investigational medicinal product code Other name Pharmaceutical forms Film-coated tablet Routes of administration details: Placebo (matched to IVA) Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product code Other name Kalydeco Pharmaceutical forms Routes of administration details: Placebo (matched to IVA) <td>Pharmaceutical forms</td> <td>Film-coated tablet</td>	Pharmaceutical forms	Film-coated tablet	
Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product code VX-770 Other name Kalydeco Pharmaceutical forms Film-coated tablet Routes of administration details: IVX-661 plus IVA combination and placebo matched to IVA in the morning, placebo matched to IVA-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 1 foliowed by VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 1 foliowed by VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period vas separated by a minimum 8 weeks of washout period. Arm type Placebo Investigational medicinal product name Placebo (matched to IVA-661 Plus IVA combination) Investigational medicinal product name Placebo (matched to IVA-661 Plus IVA combination) Investigational medicinal product name Placebo (matched to IVA-661 Plus IVA combination) Investigational medicinal product name Placebo (matched to IVA-661 Plus IVA Combination) Investigational medicinal product code VX-770 Other name Film-coated tablet Routes of administration details: Placebo (matched to IVA) Pharmaceutical forms Film-coated tablet Routes of administration details:	Routes of administration	Oral use	
Investigational medicinal product one Ivacaftor Investigational medicinal product code VX-770 Other name Kalydeco Pharmaceutical forms Film-coated tablet Routes of administration details: UVA in the morning and evening for 8 weeks. Arm title First Placebo, Then VX-661/IVA - Treatment 1: Placebo Arm description: Placebo matched to IVA off 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 off plus IVA combination and placebo matched to IVA off plus IVA combination and placebo matched to IVA off plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period VX-661 plus IVA combination Investigational medicinal product code Otal use Other name Placebo Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: 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:<	Dosage and administration details:		
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 IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA Placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period vas separated by a minimum 8 weeks of washout period. Arm type Placebo Investigational medicinal product code Other name Pharmaceutical forms Film-coated tablet Routes of administration details: Placebo (matched to IVA) Placebo antched to VX-661 plus IVA FDC in the morning for 8 weeks. Placebo Investigational medicinal product code VX-770 Other name Kalydeco Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebo Placebo attched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigat	Placebo matched to VX-661 plus IVA FD	C in the morning for 8 weeks.	
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, IVA in the evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA Arm type Placebo Investigational medicinal product name Placebo Investigational medicinal product code Otal use Other name Placebo Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebo Investigational medicinal product code Other name Pharmaceutical forms Film-coated tablet Routes of administration details: Placebo (matched to IVA) Investigational medicinal product code VX-770 Other name Placebo (matched to IVA) Pharmaceutical forms Film-coated tablet Routes of administration details: Placebo (matched to I	Investigational medicinal product name	Ivacaftor	
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 evening for 8 weeks in treatment period 1. followed by VX-661 plus IVA combination and 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 name Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebo (matched to IVA) Investigational medicinal product name Film-coated tablet Routes of administration Oral use Dosage and administration Oral use Dosage and administration Oral	Investigational medicinal product code	VX-770	
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 vas 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 Oral use Dosage and administration Oral use Dosage and administration details: Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product code VX-770 Otral use Dosage and administration Investigational medicinal product code VX-770 Other name Kalydeco Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration Oral	Other name	Kalydeco	
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, 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 evening for 8 weeks in treatment period 2. Each treatment period vas 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 name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to IVA) Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebo (matched to IVA) 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 VX-661 plus IVA combination and placebo matched to IVA in the morning, placebo mat	Pharmaceutical forms	Film-coated tablet	
IVA in the moming and evening for 8 weeks. Arm title First Placebo, Then VX-661/IVA - Treatment 1: Placebo Arm description: 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 evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and placebo matched to IVA in the evening for 8 weeks in treatment period 2. Each treatment period weeks in treatment period 2. Each treatment period weeks are provided to VX-661 Plus IVA Combination) Investigational medicinal product code Placebo Other name Placebo Pharmaceutical forms Film-coated tablet Routes of administration details: Placebo (matched to IVA) Investigational medicinal product code VX-770 Other name Film-coated tablet Routes of administration details: Placebo (matched to IVA) Investigational medicinal product code VX-770 Other name Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebo (matched to IVA - Treatment 1: Placebo Arm title First Placebo, Then IVA - Treatment 1: Placebo Arm title First Placebo, Then IVA - Treatment 1: Placebo Arm type Placebo	Routes of administration	Oral use	
Arm title First Placebo, Then VX-661/IVA - Treatment 1: Placebo Arm description: 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 evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and 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 Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code 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, IVA in the avening for 8 weeks. Arm title First Placebo, Then IVA - Treatment 1: Placebo Arm title First	Dosage and administration details:		
Arm title First Placebo, Then VX-661/IVA - Treatment 1: Placebo Arm description: 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 evening for 8 weeks in treatment period 1 followed by VX-661 plus IVA combination and 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 Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code 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, IVA in the avening for 8 weeks. Arm title First Placebo, Then IVA - Treatment 1: Placebo Arm title First	-	eks.	
Arm description: Placebo matched to VX-661 plus IVA combination and 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 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 aproduct name Placebo (matched to IVA) Investigational medicinal product code VX-700 Other 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, Then IVA - Treatment 1: Placebo			
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 Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product code Other name Placebo (matched to IVA) Investigational medicinal product code Other name Placebo (matched to IVA) Investigational medicinal product code Other name Placebo (matched to IVA) Investigational medicinal product code Other name Film-coated tablet Routes of administration Oral use Dosage and 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, JVA 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 code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX	Arm description :		
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 (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Dosage and 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 name Placebo (matched to IVA) Investigational medicinal product code VX-770 Other name Kalydeco Pharmaceutical forms Film-coated tablet Routes of 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 IVA in the morning and evening for 8 weeks. Arm title First Placebo, Then IVA - Treatment 1: Placebo matched to IVA in the evening for 8 weeks of washout period 2. Each treatment period was separated by a minimum 8 weeks of washout period 2. Each treatment period was separated by a minimum 8 weeks of washout period 2. Each treatment period was separated by a minimum 8 weeks of washout period 2. Each treatment period vas film-coated tablet Routes of administration details: Placebo (matched to VX-661 plus IVA Combination) Investigational medicinal product name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to	·		
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 Oral use Other name 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 Dosage and administration Oral use Oral use Obage and administration Oral use Dosage and administration Oral use Obage and administration Oral use Obage and administration Oral use Dosage and 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 title First Placebo matched to 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 vas separated by a minimum 8 weeks of washout period. Arm type Placebo 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		
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 IVA-661 plus IVA combination and placebo matched to 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 code Other name Investigational medicinal product code Other name Placebo Investigational medicinal product code Oral use Dosage and administration Oral use Dosage and administration	Arm type	Placebo	
Other name Film-coated tablet 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 IVA in the evening for 8 weeks in treatment period 1 followed by IVA and 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 code Other name Film-coated tablet Routes of administration Oral use Dosage and administration Oral use	Investigational medicinal product name	Placebo (matched to VX-661 Plus IVA Combination)	
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 Investigational medicinal product code Oral use Obseque and administration Oral use Dosage and administration Oral use Dosade and medicinal product code Oral use Descipational medicinal product code Oral use	Investigational medicinal product code		
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 IVA-661 plus IVA combination and 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 ovening for 8 weeks of washout period. Arm type Placebo Investigational medicinal product code Oral use Other name Placebo Investigational medicinal product code Oral use Other name Placebo Investigational medicinal product code Oral use Obage and administration Oral use Dosage and administration Oral use Pharmaceutical forms Film-coated ta	Other name		
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 IVA in the evening for 8 weeks in treatment period 1 followed by IVA and 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 Placebo Investigational medicinal product code Other name Other name Placebo Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dosage and administration Oral use Dosage and administration Oral use Dosage and administration Oral use <	Pharmaceutical forms	Film-coated tablet	
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 IVA in the morning, IVA combination and placebo matched to IVA in the morning, placebo matched to 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 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 code Other name Other name Film-coated tablet Routes of administration Oral use Dosage and administration details: Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Other name Pharmaceutical for	Routes of administration	Oral use	
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. Arm type Placebo Investigational medicinal product code Placebo Other name Placebo Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dasage and administration Oral use Directoo Investigational medicinal product code Other name Placebo Investigational medicinal product code Oral use Dosage and administration Oral use Dosage and administration details: Pl	Dosage and administration details:		
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. Arm type Placebo Investigational medicinal product code Placebo Other name Placebo Pharmaceutical forms Film-coated tablet Routes of administration Oral use Dasage and administration Oral use Directoo Investigational medicinal product code Other name Placebo Investigational medicinal product code Oral use Dosage and administration Oral use Dosage and administration details: Pl	-	C in the morning for 8 weeks.	
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 name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) <t< td=""><td>Investigational medicinal product name</td><td>Placebo (matched to IVA)</td></t<>	Investigational medicinal product name	Placebo (matched to IVA)	
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 Investigational medicinal product name Placebo Oral use Dosage and administration Oral use Oral use Dase of administration details: Placebo Investigational medicinal product code Other name Pharmaceutical forms Film-coated tablet Routes of 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 name Placebo (matched to IVA) Investigational medicinal product name Placebo (m			
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 IVA-661 Plus IVA Combination) Investigational medicinal product code Oral use Dosage and administration details: Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name P	·	Kalydeco	
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. Arm type Placebo Investigational medicinal product name Placebo (matched to VX-661 Plus IVA Combination) Investigational medicinal product code Otral use Other name Film-coated tablet Routes of administration details: Placebo (matched to IVA) Placebo matched to VX-661 plus IVA Combination Oral use Dosage and administration details: Placebo (matched to IVX-661 Plus IVA Combination) Investigational medicinal product name Film-coated tablet Routes of administration details: Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product c	Pharmaceutical forms		
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 details: Placebo (matched to IVA) Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product name Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product name Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product code Other name Placebo (matched to IVA) Investigational medicinal product code VX-770 Other name Kalydeco			
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 IVA) Investigational medicinal product name Placebo (matched to IVA) Investigational medicinal product name Placebo (matched to IVA) Other name V Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks. Investigational medicinal product name Placebo (matched to IVA) Other name V-770 Other name Kalydeco			
Arm titleFirst Placebo, Then IVA - Treatment 1: PlaceboArm 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 typePlaceboInvestigational medicinal product namePlacebo (matched to VX-661 Plus IVA Combination)Investigational medicinal product codeOther namePharmaceutical formsFilm-coated tabletRoutes of administrationOral useDosage and administration details:Placebo (matched to IVA)Investigational medicinal product namePlacebo (matched to IVA)Investigational medicinal product nameMarket (Market Tablet)Cober nameMarket (Market Tablet)Routes of administrationOral useDosage and administration details:Placebo (matched to IVA)Investigational medicinal product codeVX-770Other nameKalydeco	5	and evening for 8 weeks.	
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 typePlaceboInvestigational medicinal product namePlacebo (matched to VX-661 Plus IVA Combination)Investigational medicinal product codeOther nameOther namePlaceboPlacebo matched to VX-661 plus IVA FDC in the morning for 8 weeks.Investigational medicinal product namePlacebo (matched to IVA)Investigational medicinal product nameKalydeco		-	
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 typePlaceboInvestigational medicinal product namePlacebo (matched to VX-661 Plus IVA Combination)Investigational medicinal product codeOther nameOther namePlaceboPharmaceutical formsFilm-coated tabletRoutes of administrationOral useDosage and administration details:Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks.Investigational medicinal product codeVX-651 plus IVA Combination product codeOther namePlacebo matched to VX-661 plus IVA FDC in the morning for 8 weeks.Investigational medicinal product codeVX-770Other nameKalydeco			
Investigational medicinal product namePlacebo (matched to VX-661 Plus IVA Combination)Investigational medicinal product codeOther namePharmaceutical formsFilm-coated tabletRoutes of administrationOral useDosage and administration details:Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks.Investigational medicinal product namePlacebo (matched to IVA)Investigational medicinal product codeVX-770Other nameOther nameKalydeco	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.		
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			
Other name Film-coated tablet 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 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			
Routes of administrationOral useDosage and administration details:Placebo matched to VX-661 plus IVA FDC in the morning for 8 weeks.Investigational medicinal product namePlacebo (matched to IVA)Investigational medicinal product codeVX-770Other nameKalydeco		Film-coated tablet	
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			
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			
Investigational medicinal product namePlacebo (matched to IVA)Investigational medicinal product codeVX-770Other nameKalydeco	-		
Investigational medicinal product code VX-770 Other name Kalydeco		-	
Other name Kalydeco			
Pharmaceutical forms Film-coated tablet			
	Pharmaceutical forms	Film-coated tablet	

Period 2

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

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.

Experimental
Placebo (matched to VX-661 Plus IVA Combination)
Film-coated tablet
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
Decade and administration details	

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.

i	
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 a	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 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.

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

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 f	or 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:	
matched to IVA in the evening for 8 wee	nbination and placebo matched to IVA in the morning, placebo ks in treatment period 1 followed by IVA and placebo matched norning, IVA in the evening for 8 weeks in treatment period 2. 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 FD	C 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	-	-	-

Reporting groups			
Reporting group title	First VX-661/IVA, Th	en IVA - Treatment 1	: VX-661/IVA
Reporting group description:	•		
VX-661 plus IVA combination and placeb weeks in treatment period 1 followed by the morning, IVA in the evening for 8 we separated by a minimum 8 weeks of was	IVA and placebo mate	ched to VX-661 plus I	VA combination in
Reporting group title	First VX-661/IVA, Th	en Placebo - Treatme	nt 1: VX-661/IVA
Reporting group description:			
VX-661 plus IVA combination and placeb weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated	placebo matched to V matched to IVA in the	/X-661 plus IVA comb e evening for 8 weeks	ination and placebo
Reporting group title	First IVA, Then Place	bo - Treatment 1: IVA	4
Reporting group description:			
IVA and placebo matched to VX-661 plus weeks in treatment period 1 followed by matched to IVA in the morning, placebo 2. Each treatment period was separated	placebo matched to V matched to IVA in the	/X-661 plus IVA comb e evening for 8 weeks	ination and placebo
Reporting group title	First IVA, Then VX-6	61/IVA - Treatment 1	: IVA
Reporting group description:			
IVA and placebo matched to VX-661 plus weeks in treatment period 1 followed by the morning, IVA in the evening for 8 we separated by a minimum 8 weeks of was	VX-661 plus IVA com eks in treatment peri	bination and placebo	matched to IVA in
Reporting group title First Placebo, Then VX-661/IVA - Treatment 1: Placebo		nt 1: Placebo	
Reporting group description:	1		
Placebo matched to VX-661 plus IVA con matched to IVA in the evening for 8 wee combination and placebo matched to IVA period 2. Each treatment period was sep	ks in treatment period A in the morning, IVA	d 1 followed by VX-66 in the evening for 8 w	1 plus IVA veeks in treatment
eporting group title First Placebo, Then IVA - Treatment 1: Placebo		cebo	
Reporting group description:			
Placebo matched to VX-661 plus IVA con matched to IVA in the evening for 8 wee to VX-661 plus IVA combination in the m Each treatment period was separated by	ks in treatment period orning, IVA in the evo	d 1 followed by IVA ar ening for 8 weeks in t	nd placebo matched
Reporting group values	First VX-661/IVA, Then IVA - Treatment 1: VX-	First VX-661/IVA, Then Placebo - Treatment 1: VX-	First IVA, Then Placebo - Treatmen 1: IVA

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

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

Clinical trial results 2014-004788-18 version 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
			i
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 reporting gro	ups
Reporting group title	First VX-661/IVA, Then IVA - Treatment 1: VX-661/IVA
Reporting group description:	
weeks in treatment period 1 fol	nd placebo matched to IVA in the morning, IVA in the evening for 8 llowed by IVA and placebo matched to VX-661 plus IVA combination in g for 8 weeks in treatment period 2. Each treatment period was eks of washout period.
Reporting group title	First VX-661/IVA, Then Placebo - Treatment 1: VX-661/IVA
Reporting group description:	
weeks in treatment period 1 fol matched to IVA in the morning	nd placebo matched to IVA in the morning, IVA in the evening for 8 llowed by placebo matched to VX-661 plus IVA combination and placebo , placebo matched to IVA in the evening for 8 weeks in treatment period eparated by a minimum 8 weeks of washout period.
Reporting group title	First IVA, Then Placebo - Treatment 1: IVA
Reporting group description:	
weeks in treatment period 1 for matched to IVA in the morning	K-661 plus IVA combination in the morning, IVA in the evening for 8 llowed by placebo matched to VX-661 plus IVA combination and placebo , placebo matched to IVA in the evening for 8 weeks in treatment period reparated by a minimum 8 weeks of washout period.
Reporting group title	First IVA, Then VX-661/IVA - Treatment 1: IVA
Reporting group description:	
weeks in treatment period 1 fol	K-661 plus IVA combination in the morning, IVA in the evening for 8 llowed by VX-661 plus IVA combination and placebo matched to IVA in g for 8 weeks in treatment period 2. Each treatment period was eks of washout period.
Reporting group title	First Placebo, Then VX-661/IVA - Treatment 1: Placebo
Reporting group description:	
matched to IVA in the evening combination and placebo match	IS IVA combination and placebo matched to IVA in the morning, placebo for 8 weeks in treatment period 1 followed by VX-661 plus IVA ned to IVA in the morning, IVA in the evening for 8 weeks in treatment d 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 plu matched to IVA in the evening to VX-661 plus IVA combination	is IVA combination and placebo matched to IVA in the morning, placebo for 8 weeks in treatment period 1 followed by IVA and placebo matched in the morning, IVA in the evening for 8 weeks in treatment period 2. arated by a minimum 8 weeks of washout period.
Reporting group title	First VX-661/IVA, Then IVA - Treatment 2: IVA
Reporting group description:	
weeks in treatment period 1 fol	nd placebo matched to IVA in the morning, IVA in the evening for 8 llowed by IVA and placebo matched to VX-661 plus IVA combination in g for 8 weeks in treatment period 2. Each treatment period was eks of washout period.
Reporting group title	First VX-661/IVA, Then Placebo - Treatment 2: Placebo
Reporting group description:	
weeks in treatment period 1 for matched to IVA in the morning	nd placebo matched to IVA in the morning, IVA in the evening for 8 llowed by placebo matched to VX-661 plus IVA combination and placebo , placebo matched to IVA in the evening for 8 weeks in treatment period eparated by a minimum 8 weeks of washout period.
Reporting group title	First IVA, Then Placebo - Treatment 2: Placebo
Reporting group description:	
weeks in treatment period 1 fol matched to IVA in the morning	K-661 plus IVA combination in the morning, IVA in the evening for 8 llowed by placebo matched to VX-661 plus IVA combination and placebo , placebo matched to IVA in the evening for 8 weeks in treatment period eparated 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 Firs	st 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:
 Primary

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 information			
Timeframe for reporting advers	se 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:			
	IS IVA combination and placebo matched to IVA in the morning, placebo for 8 weeks in either treatment period 1 or 2.		
Reporting group title	le Ivacaftor		
Reporting group description:			
IVA and placebo matched to VX weeks in either treatment period	K-661 plus IVA combination in the morning, IVA in the evening for 8 of 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.

Placebo	Ivacaftor	VX-661/IVA
14 / 162 (8.64%)	10 / 157 (6.37%)	8 / 162 (4.94%)
0	0	0
0	0	0
0 / 162 (0.00%)	2 / 157 (1.27%)	0 / 162 (0.00%)
0 / 0	2 / 2	0 / 0
0 / 0	0 / 0	0 / 0
1 / 162 (0.62%)	0 / 157 (0.00%)	0 / 162 (0.00%)
0/1	0 / 0	0 / 0
0 / 0	0 / 0	0 / 0
	14 / 162 (8.64%) 0 0 0 / 162 (0.00%) 0 / 0 0 / 0 1 / 162 (0.62%) 0 / 1	14 / 162 (8.64%) 10 / 157 (6.37%) 0 0 0 0 0 0 0 0 0 0 0 2 / 157 (1.27%) 0 / 0 2 / 2 0 / 0 0 / 0 1 / 162 (0.62%) 0 / 157 (0.00%) 0 / 1 0 / 0

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			l

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
	50	10	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 occurrences (all)	9 / 162 (5.56%) 9	3 / 157 (1.91%) 3	6 / 162 (3.70%) 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

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