Clinical trial results:
A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis

Summary

EudraCT number	2018-003970-28
Trial protocol	GB BE NL DE
Global end of trial date	20 August 2020

Results information

Result version number	v2 (current)
This version publication date	19 February 2022
First version publication date	25 November 2021
Version creation reason	• New data added to full data set Updates based on NIH comment addressal

Trial information

Trial identification

Sponsor protocol code	VX18-561-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03911713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2020
Global end of trial reached?	Yes
Global end of trial date	20 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-561 in cystic fibrosis (CF) subjects.

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	17 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	77
EEA total number of subjects	15

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)	0
Adults (18-64 years)	76

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in CF subjects aged 18 years or older who have a gating mutation and were previously taking stable dose of ivacaftor (IVA).

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivacaftor

Arm description:

Subjects received IVA 150 milligrams (mg) in the treatment period for 12 weeks.

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

Dosage and administration details:

Subjects received IVA 150 mg every 12 hours (q12h).

Arm title	VX-561: 25 mg

Arm description:

Subjects received VX-561 25 mg in the treatment period for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	VX-561
Investigational medicinal product code	CTP-656
Other name	Deutivacaftor (D-IVA)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-561 25 mg once daily (qd).

Arm title	VX-561: 50 mg

Arm description:

Subjects received VX-561 50 mg in the treatment period for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	VX-561
Investigational medicinal product code	CTP-656
Other name	D-IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: Subjects received VX-561 50 mg qd.	

Arm title	VX-561: 150 mg
Arm description: Subjects received VX-561 150 mg in the treatment period for 12 weeks.	
Arm type	Experimental
Investigational medicinal product name	VX-561
Investigational medicinal product code	CTP-656
Other name	D-IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Subjects received VX-561 150 mg qd.	
Arm title	VX-561: 250 mg
Arm description: Subjects received VX-561 250 mg in the treatment period for 12 weeks.	
Arm type	Experimental
Investigational medicinal product name	VX-561
Investigational medicinal product code	CTP-656
Other name	D-IVA
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Subjects received VX-561 250 mg qd.	

Number of subjects in period 1[1]	Ivacaftor	VX-561: 25 mg	VX-561: 50 mg
Started	11	6	11
Completed	11	4	11
Not completed	0	2	0
Other	-	-	-
Lost to follow-up	-	2	-

Number of subjects in period 1[1]	VX-561: 150 mg	VX-561: 250 mg
Started	23	24
Completed	22	24
Not completed	1	0
Other	1	-
Lost to follow-up	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 77 subjects were enrolled in the study, out of those 77 subjects, 2 subjects were randomized but not dosed in the treatment period. Therefore, only 75 subjects were included in the subject disposition and baseline sections.

Baseline characteristics

Reporting groups	
Reporting group title	Ivacaftor
Reporting group description:	
Subjects received IVA 150 milligrams (mg) in the treatment period for 12 weeks.	
Reporting group title	VX-561: 25 mg
Reporting group description:	
Subjects received VX-561 25 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 50 mg
Reporting group description:	
Subjects received VX-561 50 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 150 mg
Reporting group description:	
Subjects received VX-561 150 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 250 mg
Reporting group description:	
Subjects received VX-561 250 mg in the treatment period for 12 weeks.	

Reporting group values	Ivacaftor	VX-561: 25 mg	VX-561: 50 mg
Number of subjects	11	6	11
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.3	33.0	27.8
standard deviation	± 11.7	± 10.6	± 9.0
Gender categorical Units: Subjects			
Female	4	2	3
Male	7	4	8
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	11	6	10
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	6	11
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)			
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.			
Units: percentage points			
arithmetic mean	74.0	63.6	66.8
standard deviation	± 21.2	± 22.4	± 17.4

Reporting group values	VX-561: 150 mg	VX-561: 250 mg	Total
Number of subjects	23	24	75
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	32.5	37.4	
standard deviation	± 8.5	± 11.4	-
Gender categorical			
Units: Subjects			
Female	8	9	26
Male	15	15	49
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	22	24	73
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	23	24	74
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)			
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.			
Units: percentage points			
arithmetic mean	72.6	73.9	
standard deviation	± 17.3	± 17.0	-

End points

End points reporting groups

Reporting group title	Ivacaftor
Reporting group description:	
Subjects received IVA 150 milligrams (mg) in the treatment period for 12 weeks.	
Reporting group title	VX-561: 25 mg
Reporting group description:	
Subjects received VX-561 25 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 50 mg
Reporting group description:	
Subjects received VX-561 50 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 150 mg
Reporting group description:	
Subjects received VX-561 150 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 250 mg
Reporting group description:	
Subjects received VX-561 250 mg in the treatment period for 12 weeks.	

Primary: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)[1][2]
End point description:	
FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Full analysis set (FAS) included all randomized subjects who have intended CF transmembrane conductance regulator gene (CFTR) genotype and received at least 1 dose of study drug in treatment period. VX-561:25 mg and VX-561:50 mg arms were discontinued at sponsor's discretion and it was specified in statistical plan that data will be reported for only IVA, VX-561:150 mg and VX-561:250 mg arms for this end point.	
End point type	Primary
End point timeframe:	
From Baseline at Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The results for the primary endpoint are the within group change from baseline at Week 12, for each treatment group. No between group comparison are reported.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: VX-561:25 mg and VX-561:50 mg arms were discontinued at sponsor’s discretion and were not included in mixed-effects model for repeated measures (MMRM) analysis as pre-specified in analysis plan. Therefore data are reported for IVA, VX-561:150 mg and VX-561:250 mg arms for this outcome measure.

End point values	Ivacaftor	VX-561: 150 mg	VX-561: 250 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	23	24	
Units: percentage points				
least squares mean (confidence interval 95%)	-0.8 (-6.2 to 4.7)	3.1 (-0.8 to 7.0)	2.7 (-1.0 to 6.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Sweat Chloride (SwCl)

End point title	Absolute Change in Sweat Chloride (SwCl)[3]

End point description:

Sweat samples were collected using an approved collection device. FAS. VX-561:25 mg and VX-561:50 mg arms were discontinued at sponsor's discretion and it was specified in statistical plan that data will be reported for only IVA, VX-561:150 mg and VX-561:250 mg arms for this end point.

End point type	Secondary

End point timeframe:

From Baseline at Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: VX-561:25 mg and VX-561:50 mg arms were discontinued at sponsor’s discretion and were not included in MMRM analysis as pre-specified in analysis plan. Therefore data are reported for IVA, VX-561:150 mg and VX-561:250 mg arms for this outcome measure.

End point values	Ivacaftor	VX-561: 150 mg	VX-561: 250 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	23	24	
Units: millimole per Liter (mmol/L)				
least squares mean (confidence interval 95%)	0.9 (-9.5 to 11.3)	3.3 (-4.6 to 11.2)	-6.5 (-14.2 to 1.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Pre-Dose Concentration (Ctrough) of VX-561 and Its Metabolites (M1-VX-561 and M6-VX-561) and IVA and Its Metabolites (M1-IVA and M6-IVA)

End point title	Observed Pre-Dose Concentration (Ctrough) of VX-561 and Its Metabolites (M1-VX-561 and M6-VX-561) and IVA and Its Metabolites (M1-IVA and M6-IVA)

End point description:

Pharmacokinetic (PK) set included all subjects who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. Here "Subjects Analysed" signifies those participants who were evaluable for this end point and “n” signifies those subjects those who were evaluable for the specific category. Here, "99999" (penta nine) indicates that summary statistics were not reported as the number of observations below the limit of quantification was greater than 50% of the total number of observations at the specified time points and "999999"(hexa nine) indicates "not applicable" category for respective Ctrough assessment.

End point type	Secondary

End point timeframe:
At Week 4

End point values	Ivacaftor	VX-561: 25 mg	VX-561: 50 mg	VX-561: 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	4	7	20
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
VX-561: Week 4 (n = 0, 4, 7, 20, 20)	999999 (± 999999)	26.1 (± 24.7)	123 (± 61.6)	458 (± 273)
M1-VX-561: Week 4 (n = 0, 4, 7, 20, 20)	999999 (± 999999)	18.1 (± 17.7)	108 (± 58.6)	378 (± 213)
M6-VX-561: Week 4 (n= 0, 3, 7, 20, 20)	999999 (± 999999)	99999 (± 99999)	59.8 (± 34.0)	211 (± 189)
IVA: Week 4 (n= 9, 0, 0, 0, 0)	952 (± 766)	999999 (± 999999)	999999 (± 999999)	999999 (± 999999)
M1-IVA: Week 4 (n = 9, 0, 0, 0, 0)	1330 (± 774)	999999 (± 999999)	999999 (± 999999)	999999 (± 999999)
M6-IVA: Week 4 (n = 9, 0, 0, 0, 0)	662 (± 398)	999999 (± 999999)	999999 (± 999999)	999999 (± 999999)

End point values	VX-561: 250 mg			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
VX-561: Week 4 (n = 0, 4, 7, 20, 20)	1100 (± 856)			
M1-VX-561: Week 4 (n = 0, 4, 7, 20, 20)	739 (± 407)			
M6-VX-561: Week 4 (n= 0, 3, 7, 20, 20)	370 (± 233)			
IVA: Week 4 (n= 9, 0, 0, 0, 0)	999999 (± 999999)			
M1-IVA: Week 4 (n = 9, 0, 0, 0, 0)	999999 (± 999999)			
M6-IVA: Week 4 (n = 9, 0, 0, 0, 0)	999999 (± 999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Safety Set included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 16

End point values	Ivacaftor	VX-561: 25 mg	VX-561: 50 mg	VX-561: 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	6	11	23
Units: subjects				
number (not applicable)				
Subjects with AEs	8	4	8	21
Subjects with SAEs	1	2	2	2

End point values	VX-561: 250 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: subjects				
number (not applicable)				
Subjects with AEs	23			
Subjects with SAEs	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 16	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	VX-561: 250 mg
Reporting group description: Subjects received VX-561 250 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 25 mg
Reporting group description: Subjects received VX-561 25 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 150 mg
Reporting group description: Subjects received VX-561 150 mg in the treatment period for 12 weeks.	
Reporting group title	Ivacaftor
Reporting group description: Subjects received IVA 150 mg in the treatment period for 12 weeks.	
Reporting group title	VX-561: 50 mg
Reporting group description: Subjects received VX-561 50 mg in the treatment period for 12 weeks.	

Serious adverse events	VX-561: 250 mg	VX-561: 25 mg	VX-561: 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)	2 / 6 (33.33%)	2 / 23 (8.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (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
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ivacaftor	VX-561: 50 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VX-561: 250 mg	VX-561: 25 mg	VX-561: 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 24 (83.33%)	4 / 6 (66.67%)	17 / 23 (73.91%)
General disorders and administration site conditions			
Chest discomfort			

subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	6 / 23 (26.09%)
occurrences (all)	1	2	9
Dyspnoea			
subjects affected / exposed	0 / 24 (0.00%)	2 / 6 (33.33%)	2 / 23 (8.70%)
occurrences (all)	0	2	2
Haemoptysis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 6 (0.00%)	3 / 23 (13.04%)
occurrences (all)	1	0	3
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 24 (4.17%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
Nasal congestion			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	2 / 23 (8.70%)
occurrences (all)	1	1	2
Paranasal sinus discomfort			

subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Pulmonary pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Sputum increased			
subjects affected / exposed	3 / 24 (12.50%)	0 / 6 (0.00%)	4 / 23 (17.39%)
occurrences (all)	3	0	6
Respiration abnormal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Atypical mycobacterium test positive			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Bacterial test positive			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Coronavirus test positive			

subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Protein urine present			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pulmonary function test decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Urine ketone body present			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Sinus headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Migraine			

subjects affected / exposed	1 / 24 (4.17%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 24 (4.17%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Abdominal pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Abdominal pain lower			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Duodenitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Dermatitis contact			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 24 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Musculoskeletal chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Epididymitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			

subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	4 / 24 (16.67%)	0 / 6 (0.00%)	2 / 23 (8.70%)
occurrences (all)	5	0	3
Nasopharyngitis			
subjects affected / exposed	3 / 24 (12.50%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 24 (8.33%)	0 / 6 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	1
Oral candidiasis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 6 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 6 (16.67%)	0 / 23 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Ivacaftor	VX-561: 50 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)	8 / 11 (72.73%)	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Malaise			

subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Haemoptysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Lower respiratory tract congestion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 11 (18.18%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Paranasal sinus discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pulmonary pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rales			

subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Sputum increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiration abnormal			
subjects affected / exposed	2 / 11 (18.18%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Atypical mycobacterium test positive			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Bacterial test positive			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Coronavirus test positive			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Forced expiratory volume decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Protein urine present			

subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pulmonary function test decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Urine ketone body present			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Sinus headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Abdominal pain lower			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Duodenitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Nausea			

subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Dermatitis contact			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Epididymitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Fungal skin infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 11 (18.18%)	2 / 11 (18.18%)	
occurrences (all)	2	2	

Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2019	Amended to remove VX-561: 25 mg and VX-561: 50 mg arms and updated planned efficacy and pharmacodynamic analyses. Revised the sample size and power calculation to account for increased enrollment to the VX-561: 150 mg, VX-561: 250 mg and Ivacaftor arms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported