



Clinical trial results:

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation

Summary

EudraCT number	2017-004134-29
Trial protocol	GB DE IE ES DK PL
Global end of trial date	09 September 2020

Results information

Result version number	v1
This version publication date	25 March 2021
First version publication date	25 March 2021

Trial information

Trial identification

Sponsor protocol code	VX17-659-105
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03447262
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	Vertex Pharmaceuticals Incorporated, Medical Monitor, +1 617-341-6777, medicalinfo@vrtx.com
Scientific contact	Vertex Pharmaceuticals Incorporated, Medical Monitor, +1 617-341-6777, medicalinfo@vrtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002191-PIP02-17
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2020
Global end of trial reached?	Yes
Global end of trial date	09 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) in subjects with cystic fibrosis (CF) who are homozygous or heterozygous for the F508del mutation.

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	13 July 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	United States: 262
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Ireland: 23
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	484
EEA total number of subjects	105

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)	119
Adults (18-64 years)	365
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in CF subjects aged 12 years or older who participated in parent studies VX17-659-102 (NCT03447249) and VX17-659-103 (NCT03460990). Eligible subjects from parent studies were enrolled in this study.

Period 1

Period 1 title	Triple Combination Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	VX-659/TEZ/IVA TC
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Arm description:

Subjects received VX-659/TEZ/IVA for 96 weeks in TC treatment period.

Arm type	Experimental
Investigational medicinal product name	VX-659/TEZ/IVA
Investigational medicinal product code	VX-659/VX-661/VX-770
Other name	VX-659/Tezacaftor/Ivacaftor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-659/TEZ/IVA fixed-dose combination once daily in the morning.

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 once daily in the evening.

Number of subjects in period 1 ^[1]	VX-659/TEZ/IVA TC
Started	481
Completed	2
Not completed	479
Death	2
Other	4
Adverse event	7
Study termination by sponsor	455
Withdrawal of consent (not due to AE)	2

Commercial drug is available for subject	9
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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: The total of 484 subjects were enrolled from the parent studies. Out of which, 3 subjects were enrolled but never dosed in this study. Therefore, 481 subjects are included in subject disposition and baseline sections.

Baseline characteristics

Reporting groups

Reporting group title	VX-659/TEZ/IVA TC
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Reporting group description:

Subjects received VX-659/TEZ/IVA for 96 weeks in TC treatment period.

Reporting group values	VX-659/TEZ/IVA TC	Total	
Number of subjects	481	481	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	26.9		
standard deviation	± 9.7	-	
Gender categorical			
Units: Subjects			
Female	219	219	
Male	262	262	

End points

End points reporting groups

Reporting group title	VX-659/TEZ/IVA TC
Reporting group description:	
Subjects received VX-659/TEZ/IVA for 96 weeks in TC treatment period.	

Primary: 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) ^[1]
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End point description:

End point type	Primary
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End point timeframe:

Day 1 up to 28 days after last dose of study drug or to the completion of study participation date, whichever occurs first (up to Week 100)

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: Only descriptive statistics were planned. No statistical comparisons were planned for this endpoint.

End point values	VX-659/TEZ/IVA TC			
Subject group type	Reporting group			
Number of subjects analysed	481			
Units: subjects				
Subjects with TEAEs	470			
Subjects with Serious TEAEs	99			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 28 days after last dose of study drug or to the completion of study participation date, whichever occurs first (up to Week 100)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	VX-659/TEZ/IVA TC
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Reporting group description:

Subjects received VX-659/TEZ/IVA for 96 weeks in TC treatment period.

Serious adverse events	VX-659/TEZ/IVA TC		
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 481 (20.58%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Granulomatous pneumonitis			

subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haemoptysis			
subjects affected / exposed	5 / 481 (1.04%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Increased bronchial secretion			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Breathing-related sleep disorder			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			

Device leakage			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 481 (0.83%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 481 (0.83%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Pulmonary function test decreased			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 481 (0.42%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			

subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stoma site extravasation			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Congenital, familial and genetic disorders			
Cystic fibrosis related diabetes			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac failure acute			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 481 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 481 (0.62%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 481 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Distal intestinal obstruction syndrome			

subjects affected / exposed	6 / 481 (1.25%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Duodenitis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mechanical ileus			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary colic			

subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune hepatitis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	2 / 481 (0.42%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	3 / 481 (0.62%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pelvi-ureteric obstruction			

subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis bacterial			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza			
subjects affected / exposed	2 / 481 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	4 / 481 (0.83%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

<p>Infective pulmonary exacerbation of cystic fibrosis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>40 / 481 (8.32%)</p> <p>0 / 53</p> <p>0 / 0</p>			
<p>Medical device site cellulitis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 481 (0.21%)</p> <p>0 / 1</p> <p>0 / 0</p>			
<p>Pneumonia</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>2 / 481 (0.42%)</p> <p>0 / 3</p> <p>0 / 0</p>			
<p>Pneumonia pseudomonal</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 481 (0.21%)</p> <p>0 / 1</p> <p>0 / 0</p>			
<p>Sepsis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 481 (0.21%)</p> <p>0 / 1</p> <p>0 / 0</p>			
<p>Tonsillitis</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 481 (0.21%)</p> <p>0 / 1</p> <p>0 / 0</p>			
<p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 481 (0.21%)</p> <p>0 / 1</p> <p>0 / 0</p>			
<p>Vascular device infection</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>2 / 481 (0.42%)</p> <p>0 / 2</p> <p>0 / 0</p>			
Metabolism and nutrition disorders				

Diabetes mellitus inadequate control subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia subjects affected / exposed	1 / 481 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	VX-659/TEZ/IVA TC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	446 / 481 (92.72%)		
Investigations			
Alanine aminotransferase increased subjects affected / exposed	43 / 481 (8.94%)		
occurrences (all)	55		
Blood creatine phosphokinase increased			
subjects affected / exposed	37 / 481 (7.69%)		
occurrences (all)	43		
Aspartate aminotransferase increased			
subjects affected / exposed	42 / 481 (8.73%)		
occurrences (all)	51		
Nervous system disorders			
Headache			
subjects affected / exposed	51 / 481 (10.60%)		
occurrences (all)	69		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	31 / 481 (6.44%) 34		
Pyrexia subjects affected / exposed occurrences (all)	56 / 481 (11.64%) 64		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	42 / 481 (8.73%) 51		
Vomiting subjects affected / exposed occurrences (all)	27 / 481 (5.61%) 33		
Nausea subjects affected / exposed occurrences (all)	36 / 481 (7.48%) 46		
Diarrhoea subjects affected / exposed occurrences (all)	42 / 481 (8.73%) 47		
Abdominal pain upper subjects affected / exposed occurrences (all)	26 / 481 (5.41%) 36		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	126 / 481 (26.20%) 205		
Sinus congestion subjects affected / exposed occurrences (all)	27 / 481 (5.61%) 39		
Rhinorrhoea subjects affected / exposed occurrences (all)	40 / 481 (8.32%) 50		
Respiration abnormal subjects affected / exposed occurrences (all)	28 / 481 (5.82%) 30		
Oropharyngeal pain			

subjects affected / exposed	80 / 481 (16.63%)		
occurrences (all)	106		
Nasal congestion			
subjects affected / exposed	53 / 481 (11.02%)		
occurrences (all)	66		
Sputum increased			
subjects affected / exposed	69 / 481 (14.35%)		
occurrences (all)	90		
Haemoptysis			
subjects affected / exposed	39 / 481 (8.11%)		
occurrences (all)	57		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	28 / 481 (5.82%)		
occurrences (all)	37		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	149 / 481 (30.98%)		
occurrences (all)	264		
Influenza			
subjects affected / exposed	40 / 481 (8.32%)		
occurrences (all)	45		
Upper respiratory tract infection			
subjects affected / exposed	104 / 481 (21.62%)		
occurrences (all)	178		
Sinusitis			
subjects affected / exposed	30 / 481 (6.24%)		
occurrences (all)	45		
Nasopharyngitis			
subjects affected / exposed	97 / 481 (20.17%)		
occurrences (all)	163		
Viral upper respiratory tract infection			
subjects affected / exposed	38 / 481 (7.90%)		
occurrences (all)	53		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2018	Amended to add study drug dose and tablet strength. Clarified completion of study participation and study drug interruptions and discontinuation scenarios.
23 October 2018	Amended to update stopping rules and add clarifications on descriptions for efficacy and pharmacodynamics variables.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported