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	v2 (current)
This version publication date	13 February 2022
First version publication date	25 March 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	VX17-659-105

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)	EMEA-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?	Yes

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	Australia: 49
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	United States: 262
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Ireland: 23
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 33
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 (659-102; NCT03447249) or VX17-659-103 (659-103; NCT03460990). Eligible subjects from the parent studies were enrolled in the current study VX17-659-105 (659-105).

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

Arm description:

Subjects from parent studies 659-102 or 659-103 were administered VX-659 240 milligrams (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the TC treatment period for up to 96 weeks in the current study 659-105.

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 qd 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 qd 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

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
Reporting group description:	
Subjects from parent studies 659-102 or 659-103 were administered VX-659 240 milligrams (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the TC treatment period for up to 96 weeks in the current study 659-105.	

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	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	14	
Not Hispanic or Latino	462	462	
Unknown or Not Reported	5	5	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	474	474	
More than one race	4	4	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	VX-659/TEZ/IVA TC

Reporting group description:

Subjects from parent studies 659-102 or 659-103 were administered VX-659 240 milligrams (mg) once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) in the TC treatment period for up to 96 weeks in the current study 659-105.

Subject analysis set title	VX-659/TEZ/IVA TC: Parent Study 659-102
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who either received placebo (matched to VX-659/TEZ/IVA) or VX-659/TEZ/IVA in the parent study 659-102 were administered VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the TC treatment period for up to 96 weeks in the current study 659-105.

Subject analysis set title	VX-659/TEZ/IVA TC: Parent Study 659-103
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who either received TEZ/IVA or VX-659/TEZ/IVA in the parent study 659-103 were administered
VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in the TC treatment period for up to 96 weeks in the
current study 659-105.

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]

End point description:

Open label safety set (OL-SS) included all subjects who received at least 1 dose of study drug in the current study 659-105.

End point type	Primary

End point timeframe:

From Day 1 up to 28 Days After Last Dose of Study Drug or to the Completion of Study Participation Date, Whichever
Occurs First in the Current Study 659-105 (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 AEs	470			
Subjects With SAEs	99			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for Subjects From the Parent Study 659-102

End point title	Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for Subjects From the Parent Study 659-102

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. The analysis was planned
to be reported separately for Placebo - VX-659/TEZ/IVA category (subjects who received placebo in the parent
study 659-102 and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category
(subjects who received VX-659/TEZ/IVA in both the parent study 659-102 and in the current study 659-105) as pre-specified
in analysis plan. Baseline was defined as the parent study baseline. Open label full analysis set (OL-FAS) included all rolled over subjects from the parent study 659-102 who received at least 1 dose of study drug in the current study 659-105. Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	371			
Units: percentage points				
arithmetic mean (standard deviation)				
Placebo - VX-659/TEZ/IVA (n=183)	14.2 (± 7.8)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=188)	10.3 (± 9.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in ppFEV1 for Subjects From the Parent Study 659-103

End point title	Absolute Change in ppFEV1 for Subjects From the Parent Study 659-103

End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. The analysis was planned
to be reported separately for TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in the parent study 659-103 and
VX-659-TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who
received VX-659/TEZ/IVA in both the parent study 659-103 and in the current study 659-105) as pre-specified in
analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over

subjects from the parent study 659-103 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: percentage points				
arithmetic mean (standard deviation)				
TEZ/IVA - VX-659/TEZ/IVA (n=56)	15.1 (± 11.9)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=54)	11.5 (± 9.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Sweat Chloride (SwCl) for Subjects From the Parent Study 659-102

End point title	Absolute Change in Sweat Chloride (SwCl) for Subjects From the Parent Study 659-102

End point description:

Sweat samples were collected using an approved collection device. The analysis was planned to be reported
separately for Placebo - VX-659/TEZ/IVA category (subjects who received placebo in the parent study 659-102
and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who
received VX-659/TEZ/IVA in both the parent study 659-102 and in the current study 659-105) as pre-specified in
analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-102 who received at least 1 dose of study drug in the current study 659-105. Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 24 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	371			
Units: millimole per liter (mmol/L)				
arithmetic mean (standard deviation)				
Placebo - VX-659/TEZ/IVA (n=183)	-48.9 (± 20.4)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=188)	-49.7 (± 20.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in SwCl for Subjects From the Parent Study 659-103

End point title	Absolute Change in SwCl for Subjects From the Parent Study 659-103

End point description:

Sweat samples were collected using an approved collection device. The analysis was planned to be reported
separately for TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in the parent study 659-103 and VX-659-TEZ/IVA
in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who received VX-659/TEZ/
IVA in both the parent study 659-103 and in the current study 659-105) as pre-specified in analysis plan. Baseline was
defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-103 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 24 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: mmol/L				
arithmetic mean (standard deviation)				
TEZ-IVA - VX-659/TEZ/IVA (n=56)	-45.7 (± 16.8)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=54)	-53.5 (± 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Pulmonary Exacerbations (PEx) for Subjects From the Parent Study 659-102

End point title	Number of Pulmonary Exacerbations (PEx) for Subjects From the Parent Study 659-102

End point description:

PEx was defined as treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for at least 4 sinopulmonary signs/symptoms. The analysis was planned to be reported separately for Placebo - VX-659/TEZ/IVA category (subjects who received placebo in the parent study 659-102 and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who received VX-659/TEZ/IVA in the parent study 659-102 or/and VX-659/TEZ/IVA in the current study 659-105) as pre-specified in analysis plan. Baseline was defined as the parent study baseline except for Placebo - VX-659/TEZ/IVA category, for which the baseline was defined as study 659-105 baseline. The cumulative efficacy set included subjects who received at least one dose of study drug in the parent study and/or received at least one dose of study drug in the current study 659-105. Here, "n" signifies subjects evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline up to Week 96 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	375			
Units: PEx events				
Placebo - VX-659/TEZ/IVA (n=183)	60			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=192)	84			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of PEx for Subjects From the Parent Study 659-103

End point title	Number of PEx for Subjects From the Parent Study 659-103

End point description:

PEx was defined as treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for at least 4 sinopulmonary signs/symptoms. The analysis was planned to be reported for the overall subjects from the parent study 659-103 that is combined for TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in the parent study 659-103 and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who received VX-659/TEZ/IVA in the parent study 659-103 or/and VX-659/TEZ/IVA in the current study 659-105) as pre-specified in analysis plan. Baseline was defined as the parent study baseline except for TEZ/IVA - VX-659/TEZ/IVA category, for which the baseline was defined as study 659-105 baseline. The cumulative efficacy set included subjects who received at least one dose of study drug in the parent study 659-103 and/or received at least one dose of study drug in the current study 659-105.

End point type	Secondary

End point timeframe:

From Baseline up to Week 96 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: PEx events	39			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With at Least one PEx for Subjects From the Parent Study 659-102

End point title	Number of Subjects With at Least one PEx for Subjects From the Parent Study 659-102

End point description:

Time-to-first-PEx data were planned to be estimated using Kaplan-Meier (KM) method. However, because way less than 50% subjects had event, time-to-first event data were not estimable. Instead, number of subjects with at least one PEx event was assessed and reported separately for Placebo - VX-659/TEZ/IVA category (subjects received placebo in parent study 659-102 and VX-659/TEZ/IVA in current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects received VX-659/TEZ/IVA in parent study 659-102 or/and VX-659/TEZ/IVA in current study 659-105). Baseline was defined as parent study baseline except for Placebo - VX-659/TEZ/IVA category, for which baseline was defined as study 659-105 baseline. The cumulative TC efficacy set for PEx analysis included all subjects who were randomized to VX-659/TEZ/IVA arm and received at least one dose of study drug during the parent study 659-102 and/or current study 659-105. Here, "n" signifies subjects evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline up to Week 96 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	375			
Units: subjects				
Placebo - VX-659/TEZ/IVA (n=183)	43			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=192)	52			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With at Least one PEx for Subjects From the Parent Study 659-103

End point title	Number of Subjects With at Least one PEx for Subjects From the Parent Study 659-103

End point description:

Time-to-first-PEx data were planned to be estimated using the KM method. However, because way less than 50% of subjects had events, median time-to-first-event data were not estimable. Instead, the number of subjects with at least one PEx event was assessed and reported for all subjects from the parent study 659-103, that is combined for those in the TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in the parent study 659-103 and VX-659-TEZ/IVA in the current study 659-105) and the VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who received VX-659/TEZ/IVA in the parent study 659-103 or/and in the current study 659-105). Baseline was defined as parent study baseline except for TEZ/IVA - VX-659/TEZ/IVA category, for which baseline was defined as study 659-105 baseline. The cumulative TC efficacy set for PEx analysis included subjects who were randomized to VX-659/TEZ/IVA arm and received at least one dose of study drug during the parent study and/or study 659-105.

End point type	Secondary

End point timeframe:

From Baseline up to Week 96 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: subjects	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Body Mass Index (BMI) for Subjects From the Parent Study 659-102

End point title	Absolute Change in Body Mass Index (BMI) for Subjects From the Parent Study 659-102

End point description:

BMI was defined as weight in kilograms (kg) divided by squared height in meters (m^2). The analysis was planned
to be reported separately for Placebo - VX-659/TEZ/IVA category (subjects who received placebo in the parent

study 659-102 and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category
(subjects who received VX-659/TEZ/IVA in both the parent study 659-102 and in the current study 659-105) as pre-specified
in analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-102 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	371			
Units: kilogram per meter square (kg/m^2)				
arithmetic mean (standard deviation)				
Placebo - VX-659/TEZ/IVA (n=183)	1.55 (± 1.35)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=188)	1.43 (± 1.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in BMI for Subjects From the Parent Study 659-103

End point title	Absolute Change in BMI for Subjects From the Parent Study 659-103

End point description:

BMI was defined as weight in kg divided by squared height in meters (m^2). The analysis was planned to be reported separately for TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in the parent study 659-103 and
VX-659-TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who
received VX-659/TEZ/IVA in both the parent study 659-103 and in the current study 659-105) as pre-specified in
analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-103 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: kg/m^2				
arithmetic mean (standard deviation)				
TEZ/IVA - VX-659/TEZ/IVA (n=56)	1.16 (± 1.68)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=54)	0.90 (± 1.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in BMI Z-score for Subjects From the Parent Study 659-102 (Subjects <=20 Years Old at Parent Study Baseline)

End point title	Absolute Change in BMI Z-score for Subjects From the Parent Study 659-102 (Subjects <=20 Years Old at Parent Study Baseline)

End point description:

The z-score is a statistical measure to describe whether a value was above or below the standard. A z-score of 0 is equal to the standard. Lower numbers
indicate values lower than the standard and higher numbers indicate values higher than the standard. The analysis
was planned to be reported separately for Placebo - VX-659/TEZ/IVA category (subjects who received placebo
in the parent study 659-102 and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/
IVA category (subjects who received VX-659/TEZ/IVA in both the parent study 659-102 and in the current study
659-105) as pre-specified in analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-102 who were <=20 years old at parent study baseline and received at least 1
dose of study drug in the current study 659-105. Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 60 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	114			
Units: z-score				
arithmetic mean (standard deviation)				
Placebo - VX-659/TEZ/IVA (n=57)	0.22 (± 0.59)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=57)	0.10 (± 0.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in BMI Z-score for Subjects From The Parent Study 659-103 (Subjects <=20 Years Old at Parent Study Baseline)

End point title	Absolute Change in BMI Z-score for Subjects From The Parent Study 659-103 (Subjects <=20 Years Old at Parent Study Baseline)

End point description:

The analysis was planned to be reported separately for TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in the parent
study 659-103 and VX-659-TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category
(subjects who received VX-659/TEZ/IVA in both the parent study 659-103 and in the current study 659-105) as pre-specified
in analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-103 who were <=20 years old at parent study baseline and received at least 1 dose of study drug in the current study 659-105. Here, "n" signifies subjects who were evaluable for the specified category and "99999" signifies "not available" as the summary statistics were no longer applicable for due to less than 20 subjects in each category (pre-specified criteria in analysis plan). Therefore, no BMI z-score efficacy data is available for both categories.

End point type	Secondary

End point timeframe:

From Baseline at Week 60 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: z-score				
arithmetic mean (standard deviation)				
TEZ/IVA - VX-659/TEZ/IVA (n=16)	99999 (± 99999)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=14)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Body Weight for Subjects From the Parent Study 659-102

End point title	Absolute Change in Body Weight for Subjects From the Parent Study 659-102

End point description:

The analysis was planned to be reported separately for Placebo - VX-659/TEZ/IVA category (subjects who received
placebo in the parent study 659-102 and VX-659/TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/
TEZ/IVA category (subjects who received VX-659/TEZ/IVA in both the parent study 659-102 and in the current study
659-105) as pre-specified in analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-102 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	371			
Units: kg				
arithmetic mean (standard deviation)				
Placebo - VX-659/TEZ/IVA (n=183)	4.8 (± 4.4)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=188)	4.3 (± 5.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Body Weight for Subjects From the Parent Study 659-103

End point title	Absolute Change in Body Weight for Subjects From the Parent Study 659-103

End point description:

The analysis was planned to be reported separately for TEZ/IVA - VX-659/TEZ/IVA category (subjects who received TEZ/IVA in
the parent study 659-103 and VX-659-TEZ/IVA in the current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/
IVA category (subjects who received VX-659/TEZ/IVA in both the parent study 659-103 and in the current study
659-105) as pre-specified in analysis plan. Baseline was defined as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-103 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: kg				
arithmetic mean (standard deviation)				
TEZ/IVA - VX-659/TEZ/IVA (n=56) VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=54)	3.7 (± 4.9) 3.2 (± 5.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for Subjects From the Parent Study 659-102

End point title	Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for Subjects From the Parent Study 659-102

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with
cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer
symptoms and better health-related quality of life. The analysis was planned to be reported separately for Placebo -
VX-659/TEZ/IVA category (subjects who received placebo in the parent study 659-102 and VX-659/TEZ/IVA in the
current study 659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who received VX-659/TEZ/IVA in
both the parent study 659-102 and in the current study 659-105) as pre-specified in analysis plan. Baseline was defined
as the parent study baseline. OL-FAS included all rolled over subjects from the parent study 659-102 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-102			
Subject group type	Subject analysis set			
Number of subjects analysed	371			
Units: units on a scale				
arithmetic mean (standard deviation)				

Placebo - VX-659/TEZ/IVA (n=183)	16.7 (± 18.7)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=188)	19.7 (± 17.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in CFQ-R Respiratory Domain Score for Subjects From the Parent Study 659-103

End point title	Absolute Change in CFQ-R Respiratory Domain Score for Subjects From the Parent Study 659-103

End point description:

The CFQ-R is a validated subject-reported outcome measuring health-related quality of life for subjects with
cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer
symptoms and better health-related quality of life. The analysis was planned to be reported separately for TEZ/IVA - VX-659/TEZ/IVA
category (subjects who received TEZ/IVA in the parent study 659-103 and VX-659-TEZ/IVA in the current study
659-105) and VX-659/TEZ/IVA - VX-659/TEZ/IVA category (subjects who received VX-659/TEZ/IVA in both the parent
study 659-103 and in the current study 659-105) as pre-specified in analysis plan. Baseline was defined as the parent
study baseline. OL-FAS included all rolled over subjects from the parent study 659-103 who received at least 1 dose of study drug in the current study 659-105.
Here, "n" signifies subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

From Baseline at Week 72 (Study 659-105)

End point values	VX-659/TEZ/IVA TC: Parent Study 659-103			
Subject group type	Subject analysis set			
Number of subjects analysed	110			
Units: units on a scale				
arithmetic mean (standard deviation)				
TEZ/IVA - VX-659/TEZ/IVA (n=56)	17.1 (± 18.2)			
VX-659/TEZ/IVA - VX-659/TEZ/IVA (n=54)	16.9 (± 17.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 up to 28 Days After Last Dose of Study Drug or to the Completion of Study Participation Date,
Whichever Occurs First in the Current Study 659-105 (up to Week 100)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	VX-659/TEZ/IVA TC

Reporting group description:

Subjects from parent studies 659-102 or 659-103 were administered VX-659 240 mg qd/TEZ 100 mg qd/IVA 150 mg q12h
in the TC treatment period for up to 96 weeks in the current study 659-105.

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		

Infective pulmonary exacerbation of cystic fibrosis				
subjects affected / exposed	40 / 481 (8.32%)			
occurrences causally related to treatment / all	0 / 53			
deaths causally related to treatment / all	0 / 0			
Medical device site cellulitis				
subjects affected / exposed	1 / 481 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 481 (0.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	1 / 481 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 481 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 481 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 481 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	2 / 481 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
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	31 / 481 (6.44%)		
occurrences (all)	34		
Pyrexia			
subjects affected / exposed	56 / 481 (11.64%)		
occurrences (all)	64		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	42 / 481 (8.73%)		
occurrences (all)	51		
Vomiting			
subjects affected / exposed	27 / 481 (5.61%)		
occurrences (all)	33		
Nausea			
subjects affected / exposed	36 / 481 (7.48%)		
occurrences (all)	46		
Diarrhoea			
subjects affected / exposed	42 / 481 (8.73%)		
occurrences (all)	47		
Abdominal pain upper			
subjects affected / exposed	26 / 481 (5.41%)		
occurrences (all)	36		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	126 / 481 (26.20%)		
occurrences (all)	205		
Sinus congestion			
subjects affected / exposed	27 / 481 (5.61%)		
occurrences (all)	39		
Respiration abnormal			
subjects affected / exposed	28 / 481 (5.82%)		
occurrences (all)	30		
Rhinorrhoea			
subjects affected / exposed	40 / 481 (8.32%)		
occurrences (all)	50		
Nasal congestion			

subjects affected / exposed	53 / 481 (11.02%)		
occurrences (all)	66		
Oropharyngeal pain			
subjects affected / exposed	80 / 481 (16.63%)		
occurrences (all)	106		
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		
Sinusitis			
subjects affected / exposed	30 / 481 (6.24%)		
occurrences (all)	45		
Nasopharyngitis			
subjects affected / exposed	97 / 481 (20.17%)		
occurrences (all)	163		
Upper respiratory tract infection			
subjects affected / exposed	104 / 481 (21.62%)		
occurrences (all)	178		
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