



Clinical trial results:

A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long term Treatment With VX 661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation

Summary

EudraCT number	2014-004827-29
Trial protocol	IT IE GB BE SE AT FR DK NL DE ES
Global end of trial date	05 December 2022

Results information

Result version number	v1 (current)
This version publication date	21 June 2023
First version publication date	21 June 2023

Trial information

Trial identification

Sponsor protocol code	VX14-661-110
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02565914
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)	Yes
EMA paediatric investigation plan number(s)	EMA-001640-PIP01-14
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	13 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2022
Global end of trial reached?	Yes
Global end of trial date	05 December 2022
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-661 in combination with ivacaftor(IVA) in subjects with cystic fibrosis (CF), homozygous or heterozygous for the F508del-CFTR mutation who are in the treatment Cohort.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 61
Country: Number of subjects enrolled	United Kingdom: 85
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	France: 85
Country: Number of subjects enrolled	Germany: 124
Country: Number of subjects enrolled	Ireland: 82
Country: Number of subjects enrolled	Italy: 73
Country: Number of subjects enrolled	Australia: 78
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	Israel: 31
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	United States: 402
Country: Number of subjects enrolled	Sweden: 13
Worldwide total number of subjects	1131
EEA total number of subjects	479

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)	213
Adults (18-64 years)	911
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study consists of 3 parts: Parts A, B, and C. A total of 1131 subjects were randomized in this study.

Pre-assignment

Screening details:

Subjects from Parent Studies 103 (NCT02070744), 106 (NCT02347657), 107 (NCT02516410), 108 (NCT02392234), 109 (NCT02412111) and 111 (NCT02508207), 112 (NCT02730208), 114 (NCT03150719), were enrolled in this study. This study was conducted in subjects aged 12 and older with CF who are homozygous or heterozygous for the F508del-CFTR mutation.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A: TEZ/IVA

Arm description:

Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 103, 106, 107, 108, 109 and 111 were administered TEZ 100 milligram (mg)/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.

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

Dosage and administration details:

Subjects received TEZ/IVA FDC once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Arm title	Part B: TEZ/IVA
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Arm description:

Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, 109, 112 and 114 were administered TEZ 100 mg/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.

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

Dosage and administration details:

Subjects received TEZ/IVA fixed dose once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Arm title	Part C: TEZ/IVA
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Arm description:

Subjects who received TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, and 114 were administered TEZ 100 mg/IVA 150 mg fixed dose tablet in the morning and IVA 150 mg mono tablet in the evening for 192 weeks.

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

Dosage and administration details:

Subjects received TEZ/IVA fixed dose once daily in the morning.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	VX-770
Other name	IVA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received IVA once daily in the evening.

Number of subjects in period 1	Part A: TEZ/IVA	Part B: TEZ/IVA	Part C: TEZ/IVA
Started	1044	464	204
Safety Set	1042	463	204
Completed	951	228	7
Not completed	93	236	197
Physician decision	6	1	5
Death	1	-	-
Other	18	1	-
Enrolled, but did not receive study drug	2	1	-
Adverse event	17	4	1
Study terminated by sponsor	1	-	-
Sponsor Decision	-	2	-
Lost to follow-up	12	-	-
Other non-compliance	6	-	2
Rolled over into another study	-	25	11

Withdrawal of consent (not due to AE)	25	6	4
Commercial drug is available for subject	5	196	174

Baseline characteristics

Reporting groups

Reporting group title	Part A: TEZ/IVA
Reporting group description:	
Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 103, 106, 107, 108, 109 and 111 were administered TEZ 100 milligram (mg)/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.	
Reporting group title	Part B: TEZ/IVA
Reporting group description:	
Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, 109, 112 and 114 were administered TEZ 100 mg/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.	
Reporting group title	Part C: TEZ/IVA
Reporting group description:	
Subjects who received TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, and 114 were administered TEZ 100 mg/IVA 150 mg fixed dose tablet in the morning and IVA 150 mg mono tablet in the evening for 192 weeks.	

Reporting group values	Part A: TEZ/IVA	Part B: TEZ/IVA	Part C: TEZ/IVA
Number of subjects	1044	464	204
Age categorical			
Units: Subjects			

Age continuous			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: years			
arithmetic mean	29.13	29.61	29.60
standard deviation	± 12.00	± 11.89	± 11.68
Gender categorical			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: Subjects			
Female	505	221	89
Male	539	243	115
Ethnicity			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: Subjects			
Hispanic or Latino	25	6	5
Not Hispanic or Latino	1002	437	184
Not collected per local regulations	17	21	15
Race			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: Subjects			
White	1017	447	193
Black or African American	7	1	0

Asian	2	2	1
American Indian or Alaska Native	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not collected per local regulations	11	13	10
Other	6	1	0

Reporting group values	Total		
Number of subjects	1131		
Age categorical			
Units: Subjects			

Age continuous			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: Subjects			
Female	555		
Male	576		
Ethnicity			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: Subjects			
Hispanic or Latino	25		
Not Hispanic or Latino	1077		
Not collected per local regulations	29		
Race			
There were 1131 unique subjects enrolled in the study. Out of 1044 subjects from Part A, 377 subjects is participated in Part B and 195 subjects is also participated in Part C. Out of 463 subjects from Part B, 204 subjects is participated in Part C.			
Units: Subjects			
White	1092		
Black or African American	7		
Asian	2		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	0		
Not collected per local regulations	23		
Other	6		

End points

End points reporting groups

Reporting group title	Part A: TEZ/IVA
Reporting group description: Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 103, 106, 107, 108, 109 and 111 were administered TEZ 100 milligram (mg)/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.	
Reporting group title	Part B: TEZ/IVA
Reporting group description: Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, 109, 112 and 114 were administered TEZ 100 mg/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.	
Reporting group title	Part C: TEZ/IVA
Reporting group description: Subjects who received TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, and 114 were administered TEZ 100 mg/IVA 150 mg fixed dose tablet in the morning and IVA 150 mg mono tablet in the evening for 192 weeks.	
Subject analysis set title	Part B: F/F Mutation
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received TEZ/IVA in parent studies 106, 111, 112 and 114 were received TEZ 100 mg/IVA 150 mg FDC tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.	
Subject analysis set title	Part B: F/RF Mutation
Subject analysis set type	Full analysis
Subject analysis set description: Subjects who received TEZ/IVA in parent study 108 were received TEZ 100 mg/IVA 150 mg FDC tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.	

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

End point title	Part A: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^{[1][2]}
End point description: Safety set included all subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Day 1 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

[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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	1042			
Units: Subjects				
Subjects with TEAEs	995			
Subjects with SAEs	351			

Statistical analyses

No statistical analyses for this end point

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

End point title	Part B: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[3]
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End point description:

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

End point type	Secondary
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End point timeframe:

Day 1 up to Week 100

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: This endpoint is only applicable for Part B.

End point values	Part B: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	463			
Units: Subjects				
Subjects with TEAEs	427			
Subjects with SAEs	136			

Statistical analyses

No statistical analyses for this end point

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

End point title	Part C: Safety and Tolerability as Assessed by Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[4]
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End point description:

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

End point type	Secondary
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End point timeframe:

Day 1 up to Week 196

Notes:

[4] - 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: This endpoint is only applicable for Part C.

End point values	Part C: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	204			
Units: Subjects				
Subjects with TEAEs	168			
Subjects with SAEs	44			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 106/110 Efficacy Set

End point title	Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 106/110 Efficacy Set ^[5]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[5] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	459			
Units: Percentage points				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=231)	2.1 (0.8 to 3.3)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=228)	2.0 (0.7 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 108/110 Efficacy Set

End point title	Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 108/110 Efficacy Set ^[6]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[6] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: Percentage points				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=80)	4.1 (2.2 to 6.0)			
IVA-TEZ/IVA: Change at Week 96 (n=70)	6.7 (4.7 to 8.7)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=76)	7.5 (5.6 to 9.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 103/110 Efficacy Set

End point title	Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 103/110 Efficacy Set ^[7]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported for TEZ/IVA-TEZ/IVA group (subjects who received TEZ/IVA in both parent study 103 and in current study 110). Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[7] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage points				
arithmetic mean (standard deviation)	2.7 (± 10.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 111/110 Efficacy Set

End point title	Part A: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 111/110 Efficacy Set ^[8]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 111 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 111 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[8] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage points				
arithmetic mean (standard deviation)				
Placebo-TEZ/IVA: Change at Week 96 (n=7)	4.1 (± 10.2)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=26)	2.6 (± 6.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 106/110 Efficacy Set

End point title	Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 106/110 Efficacy Set ^[9]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106

and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
End point timeframe:	
From Baseline at Study 110 Week 96	

Notes:

[9] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	459			
Units: Percent change				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=231)	4.3 (2.1 to 6.5)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=228)	4.2 (2.0 to 6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 108/110 Efficacy Set

End point title	Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 108/110 Efficacy Set ^[10]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
End point timeframe:	
From Baseline at Study 110 Week 96	

Notes:

[10] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: Percent change				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=80)	7.9 (4.7 to 11.1)			
IVA-TEZ/IVA: Change at Week 96 (n=70)	11.6 (8.2 to 15.0)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=76)	13.0 (9.7 to 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 103/110 Efficacy Set

End point title	Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 103/110 Efficacy Set ^[11]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported for TEZ/IVA-TEZ/IVA group (participants who received TEZ/IVA in both parent study 103 and in current study 110). Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[11] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percent change				
arithmetic mean (standard deviation)	6.4 (± 21.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 111/110 Efficacy Set

End point title	Part A: Relative Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1) for 111/110 Efficacy Set ^[12]
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration. Data are reported separately for Placebo-TEZ/IVA category (participants who received placebo in parent study 111 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (participants who received TEZ/IVA in both parent study 111 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[12] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percent change				
arithmetic mean (standard deviation)				
Placebo-TEZ/IVA: Change at Week 96 (n=7)	6.1 (± 14.4)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=26)	5.2 (± 11.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Pulmonary Exacerbation (PEX) Events for 106/110 PEX Analysis Set

End point title	Part A: Number of Pulmonary Exacerbation (PEX) Events for 106/110 PEX Analysis Set ^[13]
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End point description:

Pulmonary exacerbation was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline up to Study 110 Week 96

Notes:

[13] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	479			
Units: PEx events				
number (not applicable)				
Placebo-TEZ/IVA (n=231)	306			
TEZ/IVA-TEZ/IVA (n=248)	423			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Pulmonary Exacerbation (PEx) Events for 108/110 PEx Analysis Set

End point title	Part A: Number of Pulmonary Exacerbation (PEx) Events for 108/110 PEx Analysis Set ^[14]
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End point description:

Pulmonary exacerbation was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. Data are reported separately for Placebo-TEZ/IVA category (participants who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline up to Week 96

Notes:

[14] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	233			
Units: PEx events				
number (not applicable)				
Placebo-TEZ/IVA (n=81)	89			
IVA-TEZ/IVA (n=74)	51			
TEZ/IVA-TEZ/IVA (n=78)	46			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Mass Index (BMI) for 106/110 Efficacy Set

End point title	Part A: Absolute Change in Body Mass Index (BMI) for 106/110 Efficacy Set ^[15]
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End point description:

BMI was defined as weight in kilogram (kg) divided by height in square meter (m²). Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[15] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	459			
Units: kg/m ²				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=231)	0.47 (0.30 to 0.65)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=228)	0.38 (0.20 to 0.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Mass Index (BMI) for 108/110 Efficacy Set

End point title	Part A: Absolute Change in Body Mass Index (BMI) for 108/110 Efficacy Set ^[16]
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End point description:

BMI was defined as weight in kg divided by height in square meter (m²). Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[16] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: kg/m ²				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=80)	1.07 (0.59 to 1.55)			
IVA-TEZ/IVA: Change at Week 96 (n=70)	0.96 (0.45 to 1.47)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=76)	1.05 (0.56 to 1.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Mass Index (BMI) for 103/110 Efficacy Set

End point title	Part A: Absolute Change in Body Mass Index (BMI) for 103/110 Efficacy Set ^[17]
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End point description:

BMI was defined as weight in kg divided by height in square meter (m²). Data are reported for TEZ/IVA-TEZ/IVA group (subjects who received TEZ/IVA in both parent study 103 and in current study 110). Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[17] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: kg/m ²				
arithmetic mean (standard deviation)	1.38 (± 1.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Mass Index (BMI) for Study 111/110 Efficacy Set

End point title	Part A: Absolute Change in Body Mass Index (BMI) for Study 111/110 Efficacy Set ^[18]
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End point description:

BMI was defined as weight in kg divided by height in square meter (m²). Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 111 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 111 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[18] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: kg/m ²				
arithmetic mean (standard deviation)				
Placebo-TEZ/IVA: Change at Week 96 (n=7)	1.59 (± 2.08)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=26)	0.26 (± 0.88)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in BMI Z-score for 106/110 Efficacy Set

End point title	Part A: Absolute Change in BMI Z-score for 106/110 Efficacy Set ^[19]
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End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Data are reported separately for Placebo-TEZ/IVA category (participants who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[19] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: z-score				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=44)	0.10 (-0.04 to 0.25)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=49)	-0.14 (-0.28 to 0.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in BMI Z-score for 108/110 Efficacy Set

End point title	Part A: Absolute Change in BMI Z-score for 108/110 Efficacy Set ^[20]
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End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[20] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: z-score				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=13)	0.11 (-0.32 to 0.54)			
IVA-TEZ/IVA: Change at Week 96 (n=7)	0.07 (-0.52 to 0.65)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=10)	0.30 (-0.21 to 0.80)			

Statistical analyses

Secondary: Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 106/110 Efficacy Set

End point title	Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 106/110 Efficacy Set ^[21]
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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. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[21] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	459			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=231)	1.7 (-0.6 to 4.0)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=228)	3.0 (0.7 to 5.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 108/110 Efficacy Set

End point title	Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 108/110 Efficacy Set ^[22]
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End point description:

The CFQ-R is a validated participant-reported outcome measuring health-related quality of life for participants with cystic fibrosis. Respiratory domain assessed respiratory symptoms, score range: 0-100; higher scores indicating fewer symptoms and better health-related quality of life. Data are reported separately for Placebo-TEZ/IVA category (participants who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (participants who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (participants who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[22] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: units on a scale				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=80)	10.3 (7.0 to 13.6)			
IVA-TEZ/IVA: Change at Week 96 (n=70)	11.2 (7.7 to 14.7)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=76)	13.8 (10.3 to 17.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 103/110 Efficacy Set

End point title	Part A: Absolute Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain Score for 103/110 Efficacy Set ^[23]
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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. Data are reported for TEZ/IVA-TEZ/IVA group (subjects who received TEZ/IVA in both parent study 103 and in current study 110). Baseline was defined as the parent study baseline

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[23] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: units on a scale				
arithmetic mean (standard deviation)	8.6 (± 12.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Weight for Study 106/110 Efficacy Set

End point title	Part A: Absolute Change in Body Weight for Study 106/110 Efficacy Set ^[24]
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End point description:

Data are reported separately for Placebo-TEZ/IVA category (participants who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[24] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	459			
Units: kg				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=231)	2.0 (1.4 to 2.5)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=228)	2.1 (1.5 to 2.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Weight for 108/110 Efficacy Set

End point title	Part A: Absolute Change in Body Weight for 108/110 Efficacy Set ^[25]
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End point description:

Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
End point timeframe:	
From Baseline at Study 110 Week 96	
Notes:	
[25] - 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: This endpoint is only applicable for Part A.	

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	226			
Units: kg				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=80)	3.5 (1.9 to 5.1)			
IVA-TEZ/IVA: Change at Week 96 (n=70)	3.5 (1.8 to 5.2)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=76)	3.6 (2.0 to 5.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Weight for 103/110 Efficacy Set

End point title	Part A: Absolute Change in Body Weight for 103/110 Efficacy Set ^[26]
End point description:	
Data are reported for TEZ/IVA-TEZ/IVA group (subjects who received TEZ/IVA in both parent study 103 and in current study 110). Baseline was defined as the parent study baseline.	
End point type	Secondary
End point timeframe:	
From Baseline at Study 110 Week 96	
Notes:	
[26] - 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: This endpoint is only applicable for Part A.	

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: kg				
arithmetic mean (standard deviation)	4.0 (± 5.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Weight for 111/110 Efficacy Set

End point title	Part A: Absolute Change in Body Weight for 111/110 Efficacy Set ^[27]
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End point description:

Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 111 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 111 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[27] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: kg				
arithmetic mean (standard deviation)				
Placebo-TEZ/IVA: Change at Week 96 (n=7)	4.2 (± 5.7)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=26)	0.6 (± 2.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Weight Z-score for 106/110 Efficacy Set

End point title	Part A: Absolute Change in Body Weight Z-score for 106/110 Efficacy Set ^[28]
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End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[28] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: z-score				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=44)	0.07 (-0.06 to 0.20)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=49)	-0.06 (-0.19 to 0.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Body Weight Z-score for 108/110 Efficacy Set

End point title	Part A: Absolute Change in Body Weight Z-score for 108/110 Efficacy Set ^[29]
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End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[29] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: z-score				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=13)	0.15 (-0.25 to 0.55)			
IVA-TEZ/IVA: Change at Week 96 (n=7)	0.09 (-0.45 to 0.62)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=10)	0.43 (-0.04 to 0.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Height Z-score for 106/110 Efficacy Set

End point title	Part A: Absolute Change in Height Z-score for 106/110 Efficacy Set ^[30]
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End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline except for Placebo-TEZ/IVA category, for which baseline was study 110 baseline

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[30] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: z-score				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=42)	0.01 (-0.08 to 0.11)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=49)	0.13 (0.04 to 0.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Absolute Change in Height Z-score for 108/110 Efficacy Set

End point title	Part A: Absolute Change in Height Z-score for 108/110 Efficacy Set ^[31]
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End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan. Baseline was defined as the parent study baseline.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

Notes:

[31] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: z-score				
least squares mean (confidence interval 95%)				
Placebo-TEZ/IVA: Change at Week 96 (n=13)	-0.04 (-0.23 to 0.15)			
IVA-TEZ/IVA: Change at Week 96 (n=7)	0.20 (-0.05 to 0.45)			
TEZ/IVA-TEZ/IVA: Change at Week 96 (n=10)	0.23 (0.00 to 0.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Time-to-first Pulmonary Exacerbation (PEX) for 106/110 PEX Analysis Set

End point title	Part A: Time-to-first Pulmonary Exacerbation (PEX) for 106/110 PEX Analysis Set ^[32]
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End point description:

Time-to-first pulmonary exacerbation was analyzed using Kaplan-Meier estimates and expressed in terms of event-free probability. PEX was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 106 and TEZ/IVA in current study 110) and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 106 and in current study 110) as per pre-specified analysis plan.

End point type	Secondary
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End point timeframe:

96 weeks

Notes:

[32] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	479			
Units: event-free probability				
number (confidence interval 95%)				
Placebo-TEZ/IVA (n=231)	0.470 (0.402 to 0.535)			
TEZ/IVA-TEZ/IVA (n=248)	0.438 (0.374 to 0.501)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Time-to-first Pulmonary Exacerbation (PEx) for 108/110 PEx Analysis Set

End point title	Part A: Time-to-first Pulmonary Exacerbation (PEx) for 108/110 PEx Analysis Set ^[33]
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End point description:

Time-to-first pulmonary exacerbation was analyzed using Kaplan-Meier estimates and expressed in terms of event-free probability. PEx was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms. Data are reported separately for Placebo-TEZ/IVA category (subjects who received placebo in parent study 108 and TEZ/IVA in current study 110); IVA-TEZ/IVA category (subjects who received IVA monotherapy in parent study 108 and TEZ/IVA in current study 110); and TEZ/IVA-TEZ/IVA category (subjects who received TEZ/IVA in both parent study 108 and in current study 110) as per pre-specified analysis plan.

End point type	Secondary
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End point timeframe:

96 weeks

Notes:

[33] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	233			
Units: event-free probability				
number (confidence interval 95%)				
Placebo-TEZ/IVA (n=81)	0.497 (0.383 to 0.601)			
IVA-TEZ/IVA (n=74)	0.493 (0.372 to 0.603)			
TEZ/IVA-TEZ/IVA (n=78)	0.639 (0.519 to 0.737)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Plasma Concentrations of TEZ, TEZ Metabolite (M1-TEZ), Ivacaftor (IVA) and Ivacaftor Metabolite (M1-IVA)

End point title	Part A: Plasma Concentrations of TEZ, TEZ Metabolite (M1-TEZ), Ivacaftor (IVA) and Ivacaftor Metabolite (M1-IVA) ^[34]
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End point description:

The Pharmacokinetic (PK) set included data for all participants who received TEZ/IVA treatment and met PK data inclusion and exclusion criteria.

End point type	Secondary
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End point timeframe:

Week 24

Notes:

[34] - 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: This endpoint is only applicable for Part A.

End point values	Part A: TEZ/IVA			
Subject group type	Reporting group			
Number of subjects analysed	853			
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
VX-661	2070 (± 1390)			
M1-661	4580 (± 2080)			
IVA	892 (± 700)			
M1-IVA	1740 (± 1070)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)

End point title	Part B: Absolute Change in Percent Predicted Forced Expiratory Volume in 1 Second (ppFEV1)
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End point description:

FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration.

End point type	Secondary
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End point timeframe:

From Baseline at Study 110 Week 96

End point values	Part B: F/F Mutation	Part B: F/RF Mutation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	132	49		
Units: percentage points				
arithmetic mean (standard deviation)	1.7 (± 10.2)	8.3 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in Body Mass Index (BMI)

End point title Part B: Absolute Change in Body Mass Index (BMI)

End point description:

BMI was defined as weight in kilogram (kg) divided by height in square meter (m²).

End point type Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part B: F/F Mutation	Part B: F/RF Mutation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	138	60		
Units: kg/m ²				
arithmetic mean (standard deviation)	0.70 (± 1.45)	1.84 (± 2.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Absolute Change in BMI Z-score

End point title Part B: Absolute Change in BMI Z-score

End point description:

The z-score is a statistical measure to describe whether a mean was above or below the standard. A z-score of 0 is equal to the mean and is considered normal. Lower numbers indicate values lower than the mean and higher numbers indicate values higher than the mean.

End point type Secondary

End point timeframe:

From Baseline at Week 96

End point values	Part B: F/F Mutation	Part B: F/RF Mutation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	6		
Units: z-score				
arithmetic mean (standard deviation)	-0.03 (± 0.71)	0.21 (± 0.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Pulmonary Exacerbation (PEX) Events

End point title	Part B: Number of Pulmonary Exacerbation (PEX) Events
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End point description:

Pulmonary exacerbation was defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms

End point type	Secondary
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End point timeframe:

From Baseline up to Week 96

End point values	Part B: F/F Mutation	Part B: F/RF Mutation		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	347	106		
Units: PEX events				
number (not applicable)	386	94		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 Through Safety Follow-up Visit (up to Week 100 for Part A, up to Week 100 for Part B, and up to Week 196 for Part C)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Part A: TEZ/IVA
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Reporting group description:

Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 103,106,107,108,109 and 111 were administered TEZ 100 mg/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks.

Reporting group title	Part B: TEZ/IVA
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Reporting group description:

Subjects who received either TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, 109, 112 and 114 were administered TEZ 100 mg/IVA 150 mg fixed-dose tablet in the morning and IVA 150 mg mono tablet in the evening for 96 weeks

Reporting group title	Part C: TEZ/IVA
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Reporting group description:

Subjects who received TEZ/IVA, IVA monotherapy or Placebo in parent studies 106, 108, and 114 were administered TEZ 100 mg/IVA 150 mg fixed dose tablet in the morning and IVA 150 mg mono tablet in the evening for 192 weeks.

Serious adverse events	Part A: TEZ/IVA	Part B: TEZ/IVA	Part C: TEZ/IVA
Total subjects affected by serious adverse events			
subjects affected / exposed	351 / 1042 (33.69%)	136 / 463 (29.37%)	44 / 204 (21.57%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant glioma			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign male reproductive tract neoplasm			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schwannoma			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related thrombosis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Chest pain			
subjects affected / exposed	0 / 1042 (0.00%)	2 / 463 (0.43%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site erythema			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	2 / 1042 (0.19%)	2 / 463 (0.43%)	3 / 204 (1.47%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			

subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type IV hypersensitivity reaction			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gynaecomastia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial wall thickening			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Bronchiectasis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Cough			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 1042 (0.00%)	3 / 463 (0.65%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	25 / 1042 (2.40%)	10 / 463 (2.16%)	6 / 204 (2.94%)
occurrences causally related to treatment / all	0 / 32	1 / 15	0 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	2 / 1042 (0.19%)	2 / 463 (0.43%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus polyp			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sputum increased			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	5 / 1042 (0.48%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 1042 (0.19%)	1 / 463 (0.22%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disruptive mood dysregulation disorder			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranoia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			

subjects affected / exposed	3 / 1042 (0.29%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 1042 (0.29%)	1 / 463 (0.22%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 1042 (0.38%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial test positive			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Blood creatinine increased			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 1042 (0.67%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	4 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest X-ray abnormal			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Computerised tomogram thorax			

abnormal				
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Forced expiratory volume decreased				
subjects affected / exposed	3 / 1042 (0.29%)	1 / 463 (0.22%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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	
Influenza A virus test positive				
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Influenza B virus test positive				
subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Pulmonary function test decreased				
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Urine amphetamine positive				
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Respiratory syncytial virus test positive				
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Weight decreased				

subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaesthetic complication cardiac			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear injury			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Foreign body in eye			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Ligament injury			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Ligament rupture			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Meniscus injury			
subjects affected / exposed	2 / 1042 (0.19%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve injury			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural nausea			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Procedural pain			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Cardiac failure			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadrantanopia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Thrombocytopenia			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 1042 (0.67%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal mucocoele			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Colitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	8 / 1042 (0.77%)	3 / 463 (0.65%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	12 / 1042 (1.15%)	3 / 463 (0.65%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	2 / 17	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enteritis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Gastritis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	4 / 1042 (0.38%)	3 / 463 (0.65%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Nausea			

subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal achalasia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Biliary dilatation			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Cholecystitis			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder rupture			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic mass			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticarial vasculitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 1042 (0.00%)	2 / 463 (0.43%)	0 / 204 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	4 / 1042 (0.38%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Pituitary enlargement			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Musculoskeletal chest pain			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diastasis recti abdominis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Neuropathic arthropathy			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	5 / 1042 (0.48%)	1 / 463 (0.22%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterial lower respiratory tract infection			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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

Atypical mycobacterial pneumonia			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Bronchitis			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			

subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Infectious mononucleosis			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	4 / 1042 (0.38%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	243 / 1042 (23.32%)	103 / 463 (22.25%)	28 / 204 (13.73%)
occurrences causally related to treatment / all	5 / 406	0 / 169	0 / 45
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	7 / 1042 (0.67%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	7 / 1042 (0.67%)	4 / 463 (0.86%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Lung infection pseudomonal			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	1 / 1042 (0.10%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	3 / 1042 (0.29%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			

subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhoid fever			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Vascular device infection			
subjects affected / exposed	2 / 1042 (0.19%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 1042 (0.19%)	1 / 463 (0.22%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	1 / 204 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	0 / 204 (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
Hypovolaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 1042 (0.10%)	0 / 463 (0.00%)	0 / 204 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part A: TEZ/IVA	Part B: TEZ/IVA	Part C: TEZ/IVA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	938 / 1042 (90.02%)	391 / 463 (84.45%)	149 / 204 (73.04%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	53 / 1042 (5.09%)	7 / 463 (1.51%)	0 / 204 (0.00%)
occurrences (all)	61	8	0

Blood creatine phosphokinase increased			
subjects affected / exposed	76 / 1042 (7.29%)	3 / 463 (0.65%)	0 / 204 (0.00%)
occurrences (all)	90	3	0
Bacterial test positive			
subjects affected / exposed	48 / 1042 (4.61%)	28 / 463 (6.05%)	11 / 204 (5.39%)
occurrences (all)	69	43	11
Pulmonary function test decreased			
subjects affected / exposed	55 / 1042 (5.28%)	8 / 463 (1.73%)	3 / 204 (1.47%)
occurrences (all)	71	8	3
Nervous system disorders			
Headache			
subjects affected / exposed	146 / 1042 (14.01%)	47 / 463 (10.15%)	20 / 204 (9.80%)
occurrences (all)	299	147	110
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	135 / 1042 (12.96%)	40 / 463 (8.64%)	20 / 204 (9.80%)
occurrences (all)	214	58	30
Fatigue			
subjects affected / exposed	100 / 1042 (9.60%)	23 / 463 (4.97%)	7 / 204 (3.43%)
occurrences (all)	125	25	7
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	0 / 1042 (0.00%)	0 / 463 (0.00%)	15 / 204 (7.35%)
occurrences (all)	0	0	24
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	101 / 1042 (9.69%)	35 / 463 (7.56%)	7 / 204 (3.43%)
occurrences (all)	135	46	9
Abdominal pain upper			
subjects affected / exposed	44 / 1042 (4.22%)	26 / 463 (5.62%)	2 / 204 (0.98%)
occurrences (all)	51	29	2
Constipation			
subjects affected / exposed	69 / 1042 (6.62%)	24 / 463 (5.18%)	8 / 204 (3.92%)
occurrences (all)	80	25	10
Diarrhoea			

subjects affected / exposed	105 / 1042 (10.08%)	27 / 463 (5.83%)	5 / 204 (2.45%)
occurrences (all)	126	30	5
Nausea			
subjects affected / exposed	105 / 1042 (10.08%)	21 / 463 (4.54%)	9 / 204 (4.41%)
occurrences (all)	139	27	12
Vomiting			
subjects affected / exposed	80 / 1042 (7.68%)	12 / 463 (2.59%)	7 / 204 (3.43%)
occurrences (all)	105	16	9
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	99 / 1042 (9.50%)	28 / 463 (6.05%)	9 / 204 (4.41%)
occurrences (all)	124	35	11
Cough			
subjects affected / exposed	374 / 1042 (35.89%)	112 / 463 (24.19%)	29 / 204 (14.22%)
occurrences (all)	702	193	48
Haemoptysis			
subjects affected / exposed	167 / 1042 (16.03%)	64 / 463 (13.82%)	25 / 204 (12.25%)
occurrences (all)	328	105	47
Nasal congestion			
subjects affected / exposed	77 / 1042 (7.39%)	7 / 463 (1.51%)	2 / 204 (0.98%)
occurrences (all)	100	7	2
Oropharyngeal pain			
subjects affected / exposed	136 / 1042 (13.05%)	39 / 463 (8.42%)	9 / 204 (4.41%)
occurrences (all)	190	55	18
Productive cough			
subjects affected / exposed	56 / 1042 (5.37%)	15 / 463 (3.24%)	3 / 204 (1.47%)
occurrences (all)	99	22	3
Rhinorrhoea			
subjects affected / exposed	55 / 1042 (5.28%)	16 / 463 (3.46%)	1 / 204 (0.49%)
occurrences (all)	76	20	1
Sinus congestion			
subjects affected / exposed	53 / 1042 (5.09%)	2 / 463 (0.43%)	2 / 204 (0.98%)
occurrences (all)	66	2	2
Sputum increased			

subjects affected / exposed	223 / 1042 (21.40%)	46 / 463 (9.94%)	13 / 204 (6.37%)
occurrences (all)	322	64	18
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	57 / 1042 (5.47%)	23 / 463 (4.97%)	11 / 204 (5.39%)
occurrences (all)	65	24	20
Arthralgia			
subjects affected / exposed	62 / 1042 (5.95%)	29 / 463 (6.26%)	9 / 204 (4.41%)
occurrences (all)	78	38	14
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	227 / 1042 (21.79%)	88 / 463 (19.01%)	13 / 204 (6.37%)
occurrences (all)	367	133	17
Influenza			
subjects affected / exposed	62 / 1042 (5.95%)	26 / 463 (5.62%)	2 / 204 (0.98%)
occurrences (all)	67	27	2
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	444 / 1042 (42.61%)	202 / 463 (43.63%)	87 / 204 (42.65%)
occurrences (all)	977	511	192
COVID-19			
subjects affected / exposed	0 / 1042 (0.00%)	1 / 463 (0.22%)	18 / 204 (8.82%)
occurrences (all)	0	1	19
Viral upper respiratory tract infection			
subjects affected / exposed	69 / 1042 (6.62%)	15 / 463 (3.24%)	1 / 204 (0.49%)
occurrences (all)	92	21	1
Upper respiratory tract infection			
subjects affected / exposed	135 / 1042 (12.96%)	43 / 463 (9.29%)	12 / 204 (5.88%)
occurrences (all)	180	71	23
Sinusitis			
subjects affected / exposed	80 / 1042 (7.68%)	20 / 463 (4.32%)	7 / 204 (3.43%)
occurrences (all)	115	26	7
Rhinitis			
subjects affected / exposed	55 / 1042 (5.28%)	28 / 463 (6.05%)	5 / 204 (2.45%)
occurrences (all)	77	35	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2015	Amended to remove the sponsor's discretion with respect to subject discontinuation in the event of commercially available VX-661/ivacaftor.
10 March 2016	Amended to remove the age restriction for the Observational Cohort.
27 May 2016	Amended to allow subjects to screen for other qualified Vertex studies of investigational CFTR modulators while participating in the Treatment Cohort of Study VX14-661-110 and to provide the opportunity to re-enroll in the Treatment Cohort of Study VX14-661-110 for eligible subjects who discontinued Study VX14-661-110 to participate in another qualified Vertex study. The list of parent studies was revised to allow eligible subjects to enroll in the Treatment Cohort of Study VX14-661-110 from other Vertex studies investigating VX-661 in combination with ivacaftor.
24 May 2017	Amended to revise the study design to add Part B, to enroll subjects from eligible Vertex studies of VX-661 in combination with ivacaftor.
25 May 2017	Amended to add Part B, to enroll subjects from eligible Vertex studies of VX-661 in combination with ivacaftor. A Data Monitoring Committee was added to Part A. The statistical analysis plan for Part A was revised and the analysis plan for Part B was added.
25 April 2019	Amended to revise the study design to add Part C.
16 February 2021	Amended to extend the treatment duration of Part C to up to approximately 192 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported