Clinical trial results:
A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of BI 1015550 over at least 52 weeks in patients with Idiopathic Pulmonary Fibrosis (IPF)

Summary

EudraCT number	2022-001091-34
Trial protocol	IE FR ES DE NO EE FI SI PT SE NL HU BE IT GR DK HR
Global end of trial date	17 December 2024

Results information

Result version number	v1 (current)
This version publication date	02 January 2026
First version publication date	02 January 2026

Trial information

Trial identification

Sponsor protocol code	1305-0014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05321069
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 018002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 018002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 February 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2024
Global end of trial reached?	Yes
Global end of trial date	17 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of the trial was to evaluate the efficacy and safety of nerandomilast 9 mg and 18 mg bid compared with placebo in patients with IPF in addition to the patient's standard of care treatment.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 October 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 17
Country: Number of subjects enrolled	Australia: 61
Country: Number of subjects enrolled	Austria: 22
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Brazil: 23
Country: Number of subjects enrolled	Canada: 50
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	China: 97
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	France: 98
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Japan: 135
Country: Number of subjects enrolled	Malaysia: 6
Country: Number of subjects enrolled	Mexico: 7

Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Norway: 17
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 83
Country: Number of subjects enrolled	Spain: 77
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 22
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 196
Country: Number of subjects enrolled	Estonia: 5
Worldwide total number of subjects	1177
EEA total number of subjects	421

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	247
From 65 to 84 years	911
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, placebo-controlled, Phase III trial evaluating nerandomilast 9 mg and 18 mg bid vs placebo in patients with IPF. Treatment Period A lasted up to 52 weeks post-randomisation, followed by Period B with continued blinded treatment beyond 52 weeks.

Pre-assignment

Screening details:

All participants were screened for eligibility prior to participation in the trial. Participants attended a specialist site which ensured that they (the participants) strictly met all inclusion and none of the exclusion criteria. Participants were not to be allocated to a treatment sequence if any of the entry criteria were violated.

Period 1

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

Blinding implementation details:

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded regarding the randomized treatment assignments until the database is declared ready for analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matching 9 mg or 18 mg nerandomilast film coated tablet orally twice daily, with doses given at least 12 hours apart and each taken with 250 mL of water.

Arm type	Placebo
Investigational medicinal product name	Placebo matching Nerandomilast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo matching 9 mg or 18 mg Nerandomilast film coated tablet orally twice daily, with doses given at least 12 hours apart and each taken with 250 mL of water.

Arm title	Nerandomilast 9 mg BID

Arm description:

Participants received 9 mg film-coated nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.

Arm type	Experimental
Investigational medicinal product name	Nerandomilast
Investigational medicinal product code	
Other name	BI 1015550
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 9 mg film-coated Nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.

Arm title	Nerandomilast 18 mg BID

Arm description:

Participants received 18 mg film-coated nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.

Arm type	Experimental
Investigational medicinal product name	Nerandomilast
Investigational medicinal product code	
Other name	BI 1015550
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 18 mg film-coated Nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.

Number of subjects in period 1	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID
Started	393	392	392
Completed treatment period A (52 weeks)	320	324	318
Completed	292	298	299
Not completed	101	94	93
Consent withdrawn by subject	23	18	12
Adverse event, non-fatal	52	52	64
Lost to follow-up	1	-	1
No reason stated by the participants	23	22	16
Protocol deviation	1	1	-
Lack of efficacy	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching 9 mg or 18 mg nerandomilast film coated tablet orally twice daily, with doses given at least 12 hours apart and each taken with 250 mL of water.	
Reporting group title	Nerandomilast 9 mg BID
Reporting group description:	
Participants received 9 mg film-coated nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.	
Reporting group title	Nerandomilast 18 mg BID
Reporting group description:	
Participants received 18 mg film-coated nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.	

Reporting group values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID
Number of subjects	393	392	392
Age categorical			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	86	78	83
From 65-84 years	304	306	301
85 years and over	3	8	8
Age Continuous			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Years			
arithmetic mean	69.9	70.5	70.3
standard deviation	± 7.5	± 7.8	± 7.8
Sex: Female, Male			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Participants			
Female	56	75	69
Male	337	317	323
Race (NIH/OMB)			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Subjects			
American Indian or Alaska Native	1	2	2
Asian	116	121	130

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	1
White	273	266	258
More than one race	1	0	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Subjects			
Hispanic or Latino	28	23	44
Not Hispanic or Latino	365	369	348
Unknown or Not Reported	0	0	0
Forced Vital Capacity (FVC) at baseline			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Milliliters (mL)			
arithmetic mean	2863.9	2837.2	2827.3
standard deviation	± 804.6	± 781.4	± 758.0

Reporting group values	Total		
Number of subjects	1177		
Age categorical			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	247		
From 65-84 years	911		
85 years and over	19		
Age Continuous			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Participants			
Female	200		
Male	977		
Race (NIH/OMB)			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Subjects			
American Indian or Alaska Native	5		

Asian	367		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	6		
White	797		
More than one race	2		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Subjects			
Hispanic or Latino	95		
Not Hispanic or Latino	1082		
Unknown or Not Reported	0		
Forced Vital Capacity (FVC) at baseline			
Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.			
Units: Milliliters (mL)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching 9 mg or 18 mg nerandomilast film coated tablet orally twice daily, with doses given at least 12 hours apart and each taken with 250 mL of water.	
Reporting group title	Nerandomilast 9 mg BID
Reporting group description:	
Participants received 9 mg film-coated nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.	
Reporting group title	Nerandomilast 18 mg BID
Reporting group description:	
Participants received 18 mg film-coated nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.	

Primary: Absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52

End point title	Absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52
End point description:	
The absolute change from baseline in Forced Vital Capacity (FVC) [mL] at Week 52 is reported. The absolute change from baseline in forced vital capacity (FVC) at Week 52 was analyzed using a restricted maximum likelihood (REML)-based mixed model with repeated measures (MMRM). The model included fixed categorical effects of treatment and baseline antifibrotic use at each visit, as well as the continuous effect of baseline FVC. Visit was treated as a repeated measure, with an unstructured covariance structure for within-patient variability. Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug. only patients with baseline measurement and at least one post−baseline measurement are included.	
End point type	Primary
End point timeframe:	
The MMRM model is a longitudinal analysis, and it incorporated FVC measurements from baseline (Week -8 to Week -1) and Week 2, Week 6, Week 12, Week 18, Week 26, Week 36, Week 44 and Week 52. The data represent the Least Squares Mean at Week 52	

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	391	390	392	
Units: Milliliters (mL)				
least squares mean (confidence interval 95%)	-183.48 (-210.86 to -156.10)	-138.60 (-165.59 to -111.61)	-114.65 (-141.81 to -87.50)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment at each visit, baseline use of antifibrotic therapy at each visit, and fixed continuous effects of baseline forced vital capacity (FVC) in milliliters at each visit. Patients were treated as a random effect. Visit was treated as the repeated measure, and an unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	783
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	68.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.26
upper limit	107.39

Notes:

[1] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment at each visit, baseline use of antifibrotic therapy at each visit, and fixed continuous effects of baseline forced vital capacity (FVC) in milliliters at each visit. Patients were treated as a random effect. Visit was treated as the repeated measure, and an unstructured covariance structure was used to model the within-patient measurements.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.0222
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	44.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.44
upper limit	83.33

Notes:

[2] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Time to first acute IPF exacerbation or death over the duration of the trial

End point title	Time to first acute IPF exacerbation or death over the duration of the trial

End point description:

The time to first acute IPF exacerbation or death during the trial is reported as the number of participants who experienced either event.

Acute IPF is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality, with all of the following:

Acute worsening or development of dyspnea, typically of less than 1 month’s duration.

Computed tomography showing new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with IPF.

Deterioration not fully explained by cardiac failure or fluid overload.

If more than one component occurred on the same day, the patient was counted under the first event according to the following hierarchy: acute IPF exacerbation followed by death.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From first administration of any trial drug (Nerandomilast or Placebo) up to 22.9 months.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	392	392	
Units: Participants				
Acute IPF exacerbation	30	31	38	
Death	19	20	12	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.5896
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.65

Notes:

[3] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5583
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.67

Notes:

[4] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Time to hospitalization for respiratory cause or death over the duration of the trial

End point title	Time to hospitalization for respiratory cause or death over the duration of the trial

End point description:

Time to hospitalization for respiratory cause or death over the duration of the trial is reported as the number of participants who experienced either event.

Hospitalizations due to respiratory causes were recorded on a specific non-elective hospitalization CRF page. This page captured the hospitalization date, confirmation of a respiratory cause, and the primary admission diagnosis.

If more than one component occurred on the same day, the patient was counted under the first event according to the hierarchy: hospitalization for respiratory cause, followed by death.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From first administration of any trial drug (Nerandomilast or Placebo) up to 22.9 months.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	392	392	
Units: Participants				
Hospitalization for respiratory cause	59	57	68	
Death	14	11	7	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.9038
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.36

Notes:

[5] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.4687
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.56

Notes:

[6] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Time to death over the duration of the trial

End point title	Time to death over the duration of the trial

End point description:

Time to death over the duration of the trial is reported as the number of participants who died.

Time to death will be based either on the date of death on the AE report for patients with AEs leading to death or will be based on the information from the vital status assessment.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From first administration of any trial drug (Nerandomilast or Placebo) up to 22.9 months.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	392	392	
Units: Participants	28	26	21	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.4682
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.43

Notes:

[7] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.9084
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.76

Notes:

[8] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Dyspnea domain score at Week 52

End point title	Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Dyspnea domain score at Week 52

End point description:

The absolute change from baseline in the Living with Pulmonary Fibrosis (L-PF) Symptoms Dyspnea domain score at Week 52 is reported.

This endpoint was analyzed using a Mixed Model for Repeated Measures (MMRM). The model included fixed effects for treatment, baseline use of antifibrotic therapy, and baseline dyspnea score at each visit, with an unstructured covariance structure to model repeated measures.

The L-PF questionnaire is a 44-item tool consisting of two modules: Symptoms (23 items) and Impacts (21 items). The Symptoms module yields three domain scores: Dyspnea, Cough, and Fatigue, as well as a Total Symptoms score. Scoring is based on the mean of item ratings within each domain, multiplied by 100. Scores range from 0 to 100, with higher scores indicating greater impairment.

Full Analysis Set (FAS): this set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated L-PF measurements from baseline (Week -8 to Week -1) and Week 12, Week 26, Week 36, Week 44 and Week 52. The data represent the Least Squares Mean at Week 52.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	380	375	385	
Units: Score on a scale				
least squares mean (confidence interval 95%)	7.26 (5.70 to 8.82)	6.26 (4.71 to 7.80)	6.63 (5.09 to 8.17)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis used a Mixed Model for Repeated Measures (MMRM) with fixed categorical effects for treatment group and baseline antifibrotic therapy at each visit, and fixed continuous effects of baseline Living with Pulmonary Fibrosis (L-PF) Dyspnea domain score. An unstructured covariance structure accounted for within-patient correlations. Baseline antifibrotic use, as recorded in the concomitant medication case report form (CRF), was included as a covariate.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	765
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.5734
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.83
upper limit	1.57

Notes:

[9] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis used a Mixed Model for Repeated Measures (MMRM) with fixed categorical effects for treatment group and baseline antifibrotic therapy at each visit, and fixed continuous effects of baseline Living with Pulmonary Fibrosis (L-PF) Dyspnea domain score. An unstructured covariance structure accounted for within-patient correlations. Baseline antifibrotic use, as recorded in the concomitant medication case report form (CRF), was included as a covariate.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	755
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.3697
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.19

Notes:

[10] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Cough domain score at Week 52

End point title	Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Cough domain score at Week 52

End point description:

The absolute change from baseline in the L-PF Cough domain score at Week 52 is reported. This endpoint was analyzed using a Mixed Model for Repeated Measures (MMRM). The model included fixed effects for treatment, baseline antifibrotic therapy, and baseline L-PF Cough score at each visit, with an unstructured covariance matrix for repeated measures.

The Living with Pulmonary Fibrosis (L-PF) questionnaire is a 44-item tool consisting of two modules:

Symptoms (23 items) and

Impacts (21 items).

The Symptoms module yields three domain scores:

Dyspnea,

Cough, and

Fatigue,

as well as a Total Symptoms score.

Scoring is based on the mean of item ratings within each domain, multiplied by 100.

Scores range from 0 to 100, with higher scores indicating greater impairment.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated L-PF measurements from baseline (Week -8 to Week -1) and Week 12, Week 26, Week 36, Week 44 and Week 52. The data represent the Least Squares Mean at Week 52.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	379	373	385	
Units: Score on a scale				
least squares mean (confidence interval 95%)	4.54 (2.49 to 6.59)	4.44 (2.42 to 6.46)	3.95 (1.93 to 5.97)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed categorical effects for treatment group at each visit, baseline use of antifibrotic therapy at each visit,

and fixed continuous effects of the baseline Living with Pulmonary Fibrosis (L-PF) Cough domain score at each visit. An unstructured covariance structure modeled repeated measures. Baseline antifibrotic use, recorded in the concomitant medication case report form (CRF), was included as a covariate.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	764
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.6862
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	2.28

Notes:

[11] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed categorical effects for treatment group at each visit, baseline use of antifibrotic therapy at each visit, and fixed continuous effects of the baseline Living with Pulmonary Fibrosis (L-PF) Cough domain score at each visit. An unstructured covariance structure modeled repeated measures. Baseline antifibrotic use, recorded in the concomitant medication case report form (CRF), was included as a covariate.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	752
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.9442
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	2.77

Notes:

[12] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Absolute change from baseline in Forced Vital Capacity percent predicted at Week 52

End point title	Absolute change from baseline in Forced Vital Capacity percent predicted at Week 52

End point description:

The absolute change from baseline in Forced Vital Capacity percent predicted at Week 52 is reported.

Analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment at each visit, baseline use of antifibrotic therapy at each visit, and the fixed continuous effects of baseline forced vital capacity (FVC) percentage predicted at each visit. An unstructured covariance structure was used to model repeated measures within patients.
Baseline use of antifibrotic therapy, as recorded in the concomitant medication case report form (CRF)

page, was included as a covariate.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis, and it incorporated FVC measurements from baseline (Week -8 to Week -1) and Week 1, Week 2, Week 6, Week 12, Week 18, Week 26, Week 36, Week 44 and Week 52. The data represent the Least Squares Mean at Week 52.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	391	390	392	
Units: FVC percent predicted				
least squares mean (confidence interval 95%)	-4.92 (-5.67 to -4.18)	-3.75 (-4.48 to -3.01)	-3.19 (-3.93 to -2.45)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment, baseline use of antifibrotic therapy, and the fixed continuous effects of baseline forced vital capacity (FVC) percentage predicted at each visit. An unstructured covariance structure was used to model repeated measures within patients. Baseline use of antifibrotic therapy, as recorded in the concomitant medication case report form (CRF) page, was included as a covariate.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	783
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0013
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.78

Notes:

[13] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment, baseline use of antifibrotic therapy, and the fixed continuous effects of baseline forced vital capacity (FVC) percentage predicted at each visit. An unstructured covariance structure was used to model repeated measures within patients. Baseline use of antifibrotic therapy, as recorded in the concomitant medication case report form (CRF) page, was included as a covariate.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	781
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.028
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	2.22

Notes:

[14] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Fatigue domain score at Week 52

End point title	Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms Fatigue domain score at Week 52

End point description:

The absolute change from baseline in the Living with Pulmonary Fibrosis (L-PF) Fatigue domain score at Week 52 is reported.

The analysis used a mixed model for repeated measures (MMRM) with fixed categorical effects for treatment and baseline antifibrotic (AF) therapy, and the fixed continuous effect of baseline L-PF score; covariance was unstructured. Baseline AF therapy was a covariate.

The L-PF questionnaire (44 items) consists of two modules: Symptoms (23 items) and Impacts (21 items). The Symptoms module yields three domain scores (Dyspnea, Cough, Fatigue) and a Total Symptoms score. Scoring is based on the mean of item ratings within each domain, multiplied by 100. Scores range from 0 to 100, with higher scores indicating greater impairment.

The Full Analysis Set (FAS) includes all randomized patients who received at least one dose of study drug, with baseline measurement and at least one post-baseline measurement.

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated L-PF measurements from baseline (Week -8 to Week -1) and Week 12, Week 26, Week 36, Week 44 and Week 52. The data represent the Least Squares Mean at Week 52.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	380	375	386	
Units: Score on a scale				
least squares mean (confidence interval 95%)	5.40 (3.66 to 7.14)	5.59 (3.88 to 7.30)	5.82 (4.11 to 7.54)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed categorical effects for treatment group at each visit, baseline use of antifibrotic therapy at each visit, and fixed continuous effects of the baseline Living with Pulmonary Fibrosis (L-PF) Fatigue domain score at each visit. An unstructured covariance structure modeled repeated measures. Baseline antifibrotic use, recorded in the concomitant medication case report form (CRF), was included as a covariate.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	766
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.732
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	2.87

Notes:

[15] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed categorical effects for treatment group at each visit, baseline use of antifibrotic therapy at each visit, and fixed continuous effects of the baseline Living with Pulmonary Fibrosis (L-PF) Fatigue domain score at each visit. An unstructured covariance structure modeled repeated measures. Baseline antifibrotic use, recorded in the concomitant medication case report form (CRF), was included as a covariate.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	755
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.8759
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	2.63

Notes:

[16] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Key Secondary Endpoint: Time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF exacerbation, first hospitalization for respiratory cause, or death (whichever occurs first) over the duration of the trial

End point title	Key Secondary Endpoint: Time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF exacerbation, first hospitalization for respiratory cause, or death (whichever occurs first) over the duration of the trial

End point description:

Time to first occurrence of any component of the composite endpoint—acute IPF exacerbation, hospitalization for a respiratory cause, or death (whichever occurred first)—is reported as the number of participants experiencing one or more events.

Acute IPF is defined as an acute, clinically significant respiratory deterioration with: (1) dyspnea <1 month; (2) CT showing new bilateral ground-glass opacity and/or consolidation on IPF background; (3) deterioration not fully explained by cardiac failure or fluid overload. If >1 component occurred on the same day, the first event was counted in the hierarchy: acute IPF exacerbation, hospitalization, death.

The Full Analysis Set (FAS) includes all randomized patients who received ≥1 dose of study drug

End point type	Secondary

End point timeframe:

From first administration of any trial drug (Nerandomilast or Placebo) up to 22.9 months.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	392	392	
Units: Participants				
Acute IPF exacerbation as the first event	38	32	38	
Hospitalisation for respiratory cause as 1st event	49	45	47	
Death as the first event	16	13	8	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Based on Cox proportional hazards model including treatment, baseline antifibrotic therapy, age, baseline Forced Vital Capacity (FVC) percent predicted, and baseline Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) percent predicted (corrected for haemoglobin) as covariates. p-values not adjusted for multiplicity.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.9512
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.31

Notes:

[17] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The hazard ratio (HR) was estimated using a Cox proportional hazards model with treatment group, baseline antifibrotic therapy use, age (continuous), baseline FVC % predicted, and baseline DLCO % predicted (hemoglobin-corrected) as covariates. Breslow's method was applied for tied event times. A two-sided p-value from the Wald test assessed the treatment effect. P-values were not adjusted for multiplicity.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.5443
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.22

Notes:

[18] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Absolute change from baseline in Diffusing Capacity of the Lungs for Carbon Monoxide percent predicted at Week 52

End point title	Absolute change from baseline in Diffusing Capacity of the Lungs for Carbon Monoxide percent predicted at Week 52

End point description:

The absolute change from baseline in Diffusing Capacity of the Lungs for Carbon Monoxide percent predicted at Week 52 is reported.

The analysis was based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment at each visit, baseline use of antifibrotic therapy at each visit, and the fixed continuous effects of baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted at each visit. An unstructured covariance structure was used to model repeated measures within patients.
Baseline use of antifibrotic therapy, as recorded in the concomitant medication case report form (CRF) page, was included as a covariate.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

The MMRM model is a longitudinal analysis and it incorporated DLCO measurements from baseline (Week -8 to Week -1) and Week 12, Week 26, and Week 52. The data represent the Least Squares Mean at Week 52.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	380	378	384	
Units: DLCO percent predicted				
least squares mean (confidence interval 95%)	-6.14 (-7.35 to -4.94)	-3.66 (-4.85 to -2.46)	-4.47 (-5.66 to -3.27)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment, baseline use of antifibrotic therapy, and the fixed continuous effects of baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted at each visit. An unstructured covariance structure was used to model repeated measures within patients. Baseline use of antifibrotic therapy, as recorded in the concomitant medication CRF page, was included as a covariate.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	764
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.053
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	3.37

Notes:

[19] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on a Mixed Model for Repeated Measures (MMRM), which included fixed, categorical effects of treatment, baseline use of antifibrotic therapy, and the fixed continuous effects of baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted at each visit. An unstructured covariance structure was used to model repeated measures within patients. Baseline use of antifibrotic therapy, as recorded in the concomitant medication CRF page, was included as a covariate.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0042
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	4.19

Notes:

[20] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Time to absolute decline in Forced Vital Capacity (FVC) % predicted of >10% from baseline or death over the duration of the trial

End point title	Time to absolute decline in Forced Vital Capacity (FVC) % predicted of >10% from baseline or death over the duration of the trial

End point description:

The time to absolute decline of more than 10% from baseline in forced vital capacity (FVC) percent predicted, or death, over the duration of the trial is reported as the number of participants who experienced either event.
If more than one component occurred on the same day, the patient was counted under the first event according to the hierarchy; Absolute decline in FVC % predicted of > 10% followed by death.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From first administration of any trial drug (Nerandomilast or Placebo) up to 22.9 months.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	392	392	
Units: Participants				
Absolute decline in FVC % predicted of > 10%	91	89	80	
Death	20	18	14	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.2068
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.1

Notes:

[21] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.7695
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.25

Notes:

[22] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Secondary: Time to absolute decline in diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted by more than 15% from baseline or death, measured over the duration of the trial

End point title	Time to absolute decline in diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted by more than 15% from baseline or death, measured over the duration of the trial

End point description:

The time to absolute decline of more than 15% from baseline in diffusing capacity of the lungs for carbon monoxide (DLCO) percent predicted, or death, over the duration of the trial is reported as the number of participants who experienced either event.

Predicted DLCO value was corrected for hemoglobin (Hb).

If more than one component occurred on the same day, the patient was counted under the first event according to the hierarchy: Absolute decline in DLCO % predicted of > 15%, followed by Death.

Full Analysis Set (FAS): This patient set includes all randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From first administration of any trial drug (Nerandomilast or Placebo) up to 22.9 months.

End point values	Placebo	Nerandomilast 9 mg BID	Nerandomilast 18 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	393	392	392	
Units: Participants				
Absolute decline in DLCO % predicted of > 15%	38	35	43	
Death	28	24	16	

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 18 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.4988
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.26

Notes:

[23] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using a Cox proportional hazards regression model that included baseline use of antifibrotic therapy (antifibrotic group vs non-antifibrotic group), age, baseline forced vital capacity (FVC) percentage predicted, baseline diffusing capacity of the lungs for carbon monoxide (DLCO) percentage predicted (corrected for hemoglobin levels), and treatment group as covariates.

Comparison groups	Placebo v Nerandomilast 9 mg BID
Number of subjects included in analysis	785
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.9251
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.41

Notes:

[24] - The Kenward-Roger method estimated denominator degrees of freedom and adjusted standard errors; tests used two-sided α per multiple testing strategy.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE collection and All-cause mortality
From first trial drug administration (Placebo or Nerandomilast) up to 22.9 months.

Adverse event reporting additional description:

Treated Set (TS): This patient set includes all randomized patients who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo matching 9 mg or 18 mg Nerandomilast film coated tablet orally twice daily, with doses given at least 12 hours apart and each taken with 250 mL of water.

Reporting group title	Nerandomilast 9 mg BID

Reporting group description:

Participants received 9 mg film-coated Nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.

Reporting group title	Nera 18 mg BID

Reporting group description:

Participants received 18 mg film-coated Nerandomilast tablets orally twice daily, with doses administered at least 12 hours apart, each taken with 250 mL of water.

Serious adverse events	Placebo	Nerandomilast 9 mg BID	Nera 18 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	181 / 393 (46.06%)	159 / 392 (40.56%)	165 / 392 (42.09%)
number of deaths (all causes)	42	36	26
number of deaths resulting from adverse events	42	36	25
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 393 (0.25%)	5 / 392 (1.28%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 6	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atypical fibroxanthoma			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Acute leukaemia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Colon cancer			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Bladder cancer stage 0, with cancer in situ			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Bladder papilloma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Bowen's disease			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Chronic myeloid leukaemia			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Ductal adenocarcinoma of pancreas			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Extranodal marginal zone B-cell lymphoma (MALT type)			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Hodgkin's disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Laryngeal neoplasm			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Lung adenocarcinoma			

subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	3 / 393 (0.76%)	4 / 392 (1.02%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to bone			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Metastases to lung			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Rectal cancer			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 neoplasm			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	2 / 393 (0.51%)	3 / 392 (0.77%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Queyrat erythroplasia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Metastatic neoplasm			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sarcomatoid carcinoma			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Squamous cell carcinoma			
subjects affected / exposed	3 / 393 (0.76%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			

subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	4 / 393 (1.02%)	4 / 392 (1.02%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sweat gland tumour			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dilatation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Aortic aneurysm			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Aneurysm			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Arteriosclerosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vasculitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microscopic polyangiitis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery stenosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Hypovolaemic shock			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulomatosis with polyangiitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Deep vein thrombosis			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Hypotension			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Surgical and medical procedures			
Assisted suicide			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gait disturbance			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Death			
subjects affected / exposed	5 / 393 (1.27%)	4 / 392 (1.02%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 5	0 / 4	0 / 2
Condition aggravated			
subjects affected / exposed	34 / 393 (8.65%)	28 / 392 (7.14%)	32 / 392 (8.16%)
occurrences causally related to treatment / all	3 / 49	2 / 35	1 / 43
deaths causally related to treatment / all	0 / 13	1 / 6	0 / 6
Illness			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthenia			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	2 / 393 (0.51%)	3 / 392 (0.77%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent stenosis			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Anaphylactic shock			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Genital prolapse			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatomegaly			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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

Prostatitis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypersensitivity pneumonitis			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Hypercapnia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatopulmonary syndrome			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Haemothorax			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 exertional			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	7 / 393 (1.78%)	7 / 392 (1.79%)	6 / 392 (1.53%)
occurrences causally related to treatment / all	2 / 8	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Acute respiratory failure			
subjects affected / exposed	3 / 393 (0.76%)	4 / 392 (1.02%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	1 / 3	0 / 5	0 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary congestion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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	7 / 393 (1.78%)	5 / 392 (1.28%)	5 / 392 (1.28%)
occurrences causally related to treatment / all	1 / 7	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic pulmonary fibrosis			
subjects affected / exposed	12 / 393 (3.05%)	13 / 392 (3.32%)	11 / 392 (2.81%)
occurrences causally related to treatment / all	0 / 14	0 / 20	0 / 16
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 3
Interstitial lung disease			

subjects affected / exposed	2 / 393 (0.51%)	2 / 392 (0.51%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Painful respiration			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pneumomediastinum			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 393 (0.51%)	4 / 392 (1.02%)	8 / 392 (2.04%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumothorax spontaneous			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	3 / 393 (0.76%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery dilatation			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 artery thrombosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pulmonary fibrosis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary hypertension			
subjects affected / exposed	12 / 393 (3.05%)	9 / 392 (2.30%)	12 / 392 (3.06%)
occurrences causally related to treatment / all	1 / 12	0 / 9	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord leukoplakia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	9 / 393 (2.29%)	4 / 392 (1.02%)	4 / 392 (1.02%)
occurrences causally related to treatment / all	2 / 9	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Respiratory distress			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 venous hypertension			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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			
Depressive symptom			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Depression			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Alcohol abuse			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Hallucinations, mixed			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Major depression			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Tobacco abuse			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Suicidal ideation			

subjects affected / exposed	2 / 393 (0.51%)	3 / 392 (0.77%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 2	4 / 4	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus test positive			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Heart rate irregular			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
False positive investigation result			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 test positive			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interferon gamma release assay positive			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Weight decreased			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Oxygen saturation decreased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Lipase increased			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Coronary artery restenosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compression fracture			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cervical vertebral fracture			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Venomous bite			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Wrist fracture			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Skin laceration			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Rib fracture			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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 pneumothorax			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pelvic fracture			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Lower limb fracture			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Humerus fracture			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Hip fracture			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Fractured sacrum			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Fall			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Femur fracture			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Retinopathy congenital			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Acute myocardial infarction			
subjects affected / exposed	2 / 393 (0.51%)	3 / 392 (0.77%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute right ventricular failure			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Bundle branch block right			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cardiac arrest			
subjects affected / exposed	2 / 393 (0.51%)	3 / 392 (0.77%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 1
Cardiac failure			
subjects affected / exposed	3 / 393 (0.76%)	1 / 392 (0.26%)	5 / 392 (1.28%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Atrioventricular block			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 393 (0.25%)	2 / 392 (0.51%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cardiac failure chronic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery dissection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Coronary artery disease			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale chronic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cor pulmonale			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cardiogenic shock			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac valve disease			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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 failure			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 393 (0.00%)	2 / 392 (0.51%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Heart failure with reduced ejection fraction			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure with preserved ejection fraction			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Coronary artery stenosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Myocardial ischaemia			

subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular hypertrophy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	3 / 393 (0.76%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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			
Carotid artery dissection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system haemorrhage			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cerebral infarction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
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 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Ischaemic stroke			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Haemorrhagic stroke			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoplegia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 393 (0.25%)	2 / 392 (0.51%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Middle cerebral artery stroke			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal dyscognitive seizures			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Transient ischaemic attack			
subjects affected / exposed	2 / 393 (0.51%)	2 / 392 (0.51%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 393 (0.76%)	1 / 392 (0.26%)	0 / 392 (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
Subdural hygroma			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal claudication			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Presyncope			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Partial seizures			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Myelopathy			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acquired factor VIII deficiency			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Pancytopenia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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 loss anaemia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Presbyacusis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Amaurosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal infarction			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotony of eye			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Glaucoma			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry age-related macular degeneration			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Haemorrhoids			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal mass			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Intestinal obstruction			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Enteritis			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Large intestine polyp			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Tongue ulceration			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Stomatitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Pancreatitis acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Pancreatitis			

subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oronasal fistula			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Oesophagitis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal rupture			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Nausea			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Vomiting			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Varices oesophageal			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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-induced liver injury			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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	3 / 393 (0.76%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 393 (0.00%)	2 / 392 (0.51%)	0 / 392 (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
Cholangitis			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Biliary obstruction			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dilatation			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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 colic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Bile duct stone			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Suspected drug-induced liver injury			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Hepatitis toxic			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Hepatic failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Portal vein thrombosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urethral stenosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Renal impairment			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Nephrolithiasis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (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
Nephritis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			

subjects affected / exposed	3 / 393 (0.76%)	5 / 392 (1.28%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	1 / 3	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Intervertebral disc protrusion			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gouty arthritis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Chondropathy			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Arthropathy			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthralgia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Osteonecrosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 393 (0.25%)	2 / 392 (0.51%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Spinal stenosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Systemic scleroderma			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyositis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Polymyalgia rheumatica			

subjects affected / exposed	1 / 393 (0.25%)	2 / 392 (0.51%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Appendicitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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 pneumonia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterial infection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Endocarditis bacterial			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 infective			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Cellulitis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
COVID-19 pneumonia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	2 / 393 (0.51%)	4 / 392 (1.02%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cytomegalovirus infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pleurisy bacterial			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Norovirus infection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Latent tuberculosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Influenza			

subjects affected / exposed	3 / 393 (0.76%)	3 / 392 (0.77%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
HCoV-OC43 infection			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Gastroenteritis salmonella			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Gastroenteritis norovirus			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Pneumonia pseudomonal			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pneumonia viral			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 393 (0.51%)	1 / 392 (0.26%)	4 / 392 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	22 / 393 (5.60%)	18 / 392 (4.59%)	17 / 392 (4.34%)
occurrences causally related to treatment / all	4 / 26	0 / 19	0 / 18
deaths causally related to treatment / all	1 / 2	0 / 4	0 / 2
Pneumonia aspiration			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Pneumonia bacterial			
subjects affected / exposed	1 / 393 (0.25%)	6 / 392 (1.53%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	2 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 393 (0.76%)	0 / 392 (0.00%)	0 / 392 (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
Urosepsis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (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
Septic shock			
subjects affected / exposed	1 / 393 (0.25%)	2 / 392 (0.51%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	0 / 393 (0.00%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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
Dehydration			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 393 (0.25%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 393 (0.00%)	1 / 392 (0.26%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 393 (0.51%)	0 / 392 (0.00%)	0 / 392 (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
Hyperkalaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 392 (0.00%)	0 / 392 (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	Placebo	Nerandomilast 9 mg BID	Nera 18 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	316 / 393 (80.41%)	319 / 392 (81.38%)	337 / 392 (85.97%)
Investigations			
Weight decreased			
subjects affected / exposed	39 / 393 (9.92%)	45 / 392 (11.48%)	54 / 392 (13.78%)
occurrences (all)	42	59	68
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 393 (5.85%)	27 / 392 (6.89%)	28 / 392 (7.14%)
occurrences (all)	26	33	37
Dizziness			

subjects affected / exposed	21 / 393 (5.34%)	28 / 392 (7.14%)	19 / 392 (4.85%)
occurrences (all)	27	29	22
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	23 / 393 (5.85%)	35 / 392 (8.93%)	30 / 392 (7.65%)
occurrences (all)	28	39	31
Condition aggravated			
subjects affected / exposed	27 / 393 (6.87%)	19 / 392 (4.85%)	27 / 392 (6.89%)
occurrences (all)	30	21	38
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	75 / 393 (19.08%)	130 / 392 (33.16%)	166 / 392 (42.35%)
occurrences (all)	110	189	250
Vomiting			
subjects affected / exposed	19 / 393 (4.83%)	19 / 392 (4.85%)	21 / 392 (5.36%)
occurrences (all)	33	22	42
Nausea			
subjects affected / exposed	28 / 393 (7.12%)	39 / 392 (9.95%)	33 / 392 (8.42%)
occurrences (all)	39	44	41
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	79 / 393 (20.10%)	74 / 392 (18.88%)	73 / 392 (18.62%)
occurrences (all)	91	84	84
Dyspnoea			
subjects affected / exposed	58 / 393 (14.76%)	50 / 392 (12.76%)	44 / 392 (11.22%)
occurrences (all)	66	53	54
Psychiatric disorders			
Depression			
subjects affected / exposed	38 / 393 (9.67%)	42 / 392 (10.71%)	42 / 392 (10.71%)
occurrences (all)	45	49	47
Anxiety			
subjects affected / exposed	40 / 393 (10.18%)	35 / 392 (8.93%)	44 / 392 (11.22%)
occurrences (all)	49	44	48
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	17 / 393 (4.33%)	25 / 392 (6.38%)	31 / 392 (7.91%)
occurrences (all)	19	33	33
Arthralgia			
subjects affected / exposed	26 / 393 (6.62%)	23 / 392 (5.87%)	16 / 392 (4.08%)
occurrences (all)	29	25	22
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	12 / 393 (3.05%)	15 / 392 (3.83%)	23 / 392 (5.87%)
occurrences (all)	25	18	35
Pneumonia			
subjects affected / exposed	17 / 393 (4.33%)	21 / 392 (5.36%)	18 / 392 (4.59%)
occurrences (all)	21	27	21
Nasopharyngitis			
subjects affected / exposed	53 / 393 (13.49%)	46 / 392 (11.73%)	49 / 392 (12.50%)
occurrences (all)	69	58	59
COVID-19			
subjects affected / exposed	61 / 393 (15.52%)	74 / 392 (18.88%)	59 / 392 (15.05%)
occurrences (all)	61	77	60
Bronchitis			
subjects affected / exposed	37 / 393 (9.41%)	35 / 392 (8.93%)	37 / 392 (9.44%)
occurrences (all)	46	46	45
Upper respiratory tract infection			
subjects affected / exposed	47 / 393 (11.96%)	49 / 392 (12.50%)	56 / 392 (14.29%)
occurrences (all)	62	57	72
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 393 (7.12%)	39 / 392 (9.95%)	41 / 392 (10.46%)
occurrences (all)	30	41	48

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2023	In this revision of the CTP, major changes were made to address several aspects. Eligibility criteria were updated to include patients with an "alternative diagnosis" HRCT finding, and the upper DLCO limit was removed as it was not a relevant exclusion criterion. Inclusion criterion IC7 was revised to allow oral contraceptives as a highly effective method of contraception in WOCBP when combined with a barrier method, based on a drug-drug interaction trial with midazolam. A FEV/FVC ratio <0.7 was to be avoided due to the high risk of emphysema and obstruction impacting efficacy endpoints. Exclusion criterion EC10 was clarified to specify that Child Pugh refers only to liver cirrhosis, not chronic liver disease. EC23 was revised to indicate that nerandomilast was not expected to negatively affect latent TB, based on preclinical data, and TB diagnosis was simplified. A new exclusion criterion, EC27, was added for patients with a history of stem cell therapy for pulmonary fibrosis due to unknown long-term effects; such therapy was also not permitted as concomitant treatment. Guidance on managing patients and data if the 9 mg bid dose was deemed futile was clarified, considering blinding, randomisation, and interim analysis details. Restrictions on prior prednisone use were relaxed to permit historical use and use during exacerbations. Patients were to be analysed as randomised for efficacy and as treated for safety, with the PPS removed in favour of estimands per ICH E9 addendum; the FAS became the primary efficacy analysis population and the TS the primary safety population. Lastly, for time-to-event endpoints, the start date was changed from the randomisation date to the first drug intake date to accurately reflect the actual time at risk.
20 September 2023	In this revision of the CTP, major updates were introduced. The efficacy interim analysis was removed, and only the main and final analyses were specified. This decision, made by the sponsor before the futility analysis, was based on Health Authority feedback and rapid recruitment, which reduced the time benefit of conducting an interim analysis. The overall trial design section was updated accordingly to reflect these analyses. Sponsor unblinding at the main analysis (DBL1) was clarified, along with the use of unblinded PK data before DBL1 by personnel involved in PK analyses to support early preparation. It was also clarified that hypothesis testing of the key secondary endpoint would occur at the main analysis, and a high-level overview of endpoints to be assessed at both the main and final analyses was provided. Regarding concomitant treatments, restrictions on PDE inhibitors were narrowed to those specifically interfering with PDE4. Additionally, AE reporting procedures based on HADS were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported