Clinical trial results:
INBUILD®: A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

Summary

EudraCT number	2015-003360-37
Trial protocol	FR ES BE DE GB PL IT
Global end of trial date	12 August 2019

Results information

Result version number	v2 (current)
This version publication date	11 January 2022
First version publication date	23 August 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1199.247

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02999178
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, QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, +1 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 18002430127, 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	11 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2019
Global end of trial reached?	Yes
Global end of trial date	12 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the current study was to investigate the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD) defined as patients who present with features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT) and whose lung function and respiratory symptoms or chest imaging have worsened despite treatment with unapproved medications used in clinical practice to treat ILD. There is currently no efficacious treatment available for PF-ILD. Based on its efficacy and safety in Idiopathic Pulmonary Fibrosis (IPF), it is anticipated that Nintedanib will be a new treatment option for patients with PF-ILD.

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	17 January 2017
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	China: 25
Country: Number of subjects enrolled	Japan: 166
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 39
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 211
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Germany: 79
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	France: 87
Country: Number of subjects enrolled	United Kingdom: 43
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Poland: 43
Country: Number of subjects enrolled	Russian Federation: 55
Country: Number of subjects enrolled	Argentina: 43
Country: Number of subjects enrolled	Chile: 52

Worldwide total number of subjects	1010
EEA total number of subjects	359

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)	404
From 65 to 84 years	593
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Randomised (1:1 ratio), placebo-controlled, double-blind, parallel-group trial comparing nintedanib to placebo over a 52-week treatment period (Part A). Subjects continued on blinded, randomised treatment beyond 52 weeks (Part B). Data base lock (DBL) one was on 6-June-2019, DBL two was on 11-September-2019. Overall Study Period=Part A and B.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group 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	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	150 mg Nintedanib

Arm description:

150 milligram (mg) Nintedanib as soft gelatine capsule, administered orally, twice daily (bid), with optional dose reduction to 100 mg bid to manage adverse events (AEs). Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

150 milligram (mg) Nintedanib as soft gelatine capsule, administered orally, twice daily (bid), with optional dose reduction to 100 mg bid to manage adverse events (AEs). Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Arm title	Placebo

Arm description:

150 mg Nintedanib matching placebo, soft gelatine capsule, administered orally, bid, with optional dose reduction to 100 mg bid to manage AEs. Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

150 mg Nintedanib matching placebo, soft gelatine capsule, administered orally, bid, with optional dose reduction to 100 mg bid to manage AEs. Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Number of subjects in period 1[1]	150 mg Nintedanib	Placebo
Started	332	331
Completed	218	231
Not completed	114	100
Other reason not defined above	7	13
Adverse event, serious fatal	15	30
Consent withdrawn by subject	21	21
Adverse event, non-fatal	70	32
Lost to follow-up	-	2
Protocol deviation	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	150 mg Nintedanib
Reporting group description:	
150 milligram (mg) Nintedanib as soft gelatine capsule, administered orally, twice daily (bid), with optional dose reduction to 100 mg bid to manage adverse events (AEs). Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).	
Reporting group title	Placebo
Reporting group description:	
150 mg Nintedanib matching placebo, soft gelatine capsule, administered orally, bid, with optional dose reduction to 100 mg bid to manage AEs. Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).	

Reporting group values	150 mg Nintedanib	Placebo	Total
Number of subjects	332	331	663
Age categorical			
Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
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)	139	121	260
From 65-84 years	189	205	394
85 years and over	4	5	9
Age Continuous			
Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
Units: years			
arithmetic mean	65.2	66.3	
standard deviation	± 9.7	± 9.8	-
Sex: Female, Male			
Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
Units:			
Female	153	154	307
Male	179	177	356
Race (NIH/OMB)			
Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	83	80	163

Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	5	5	10
White	242	246	488
More than one race	1	0	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
Units: Subjects			
Hispanic or Latino	47	49	96
Not Hispanic or Latino	285	282	567
Unknown or Not Reported	0	0	0
Baseline High Resolution Computed Tomography (HRCT) fibrotic pattern			
HRCT fibrotic pattern, i.e. imaging pattern of the lung disease on high-resolution computed tomography assessed by central review. HRCT fibrotic pattern had two categories: 'Usual Interstitial Pneumonia (UIP)-like fibrotic pattern only', 'Other fibrotic patterns'. Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
Units: Subjects			
UIP-like fibrotic pattern only	206	206	412
Other fibrotic patterns	126	125	251
Baseline Forced Vital Capacity (FVC) - Overall Population			
FVC is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Subject set (=Treated set): This set included all randomised subjects who received at least 1 dose of trial medication.			
Units: Milliliter (mL)			
arithmetic mean	2340.07	2321.15	
standard deviation	± 740.19	± 727.97	-
Baseline FVC - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only			
FVC is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Subject set (=Treated set): This set included all randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication. The arithmetic mean and Standard Deviation shown in the table below are based on: 206 subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern treated with 150 mg Nintedanib, 206 subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern treated with Placebo.			
Units: Milliliter (mL)			
arithmetic mean	2363.43	2373.59	
standard deviation	± 762.89	± 720.05	-

End points

End points reporting groups

Reporting group title	150 mg Nintedanib

Reporting group description:

150 milligram (mg) Nintedanib as soft gelatine capsule, administered orally, twice daily (bid), with optional dose reduction to 100 mg bid to manage adverse events (AEs). Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Reporting group title	Placebo

Reporting group description:

150 mg Nintedanib matching placebo, soft gelatine capsule, administered orally, bid, with optional dose reduction to 100 mg bid to manage AEs. Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, subjects continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Primary: Annual rate of decline in Forced Vital Capacity - Overall population

End point title	Annual rate of decline in Forced Vital Capacity - Overall population

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Overall population consists of all randomized subjects with High Resolution Computed Tomography (HRCT) fibrotic pattern=UIP-like fibrotic pattern only or HRCT fibrotic pattern= Other fibrotic patterns. Annual rate of decline in Forced Vital Capacity in milliliter (mL) per year in the overall population is based on a random coefficient regression with fixed effects for treatment, HRCT fibrotic pattern, and baseline FVC [mL], and including treatment−by−time and baseline−by−time interactions. Within−subject errors are modelled by an unstructured variance−covariance matrix.

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Primary

End point timeframe:

Baseline, 2, 4, 6, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[1]	331[2]		
Units: Milliliter per year				
least squares mean (confidence interval 95%)	-80.82 (-110.42 to -51.22)	-187.78 (-216.92 to -158.64)		

Notes:

[1] - Overall Population

[2] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The decrease in FVC was assumed to be linear within each participant over 52 weeks. The intercepts and slopes were assumed to be
normally distributed with unstructured covariance matrix. The within participant error was assumed to be independent and normally
distributed with mean 0 and a common variance. The Kenward-Roger approximation was used to estimate denominator degrees of
freedom and adjust standard errors (SEs).

Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted annual rates
Point estimate	106.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	65.42
upper limit	148.5
Variability estimate	Standard error of the mean
Dispersion value	21.15

Notes:

[3] - Fixed effects: Treatment, HRCT fibrotic pattern, baseline FVC (mL), treatment-by-time, baseline-by-time interactions. Random effects: time, intercept. Difference of adjusted annual rates of decline was calculated as Nintedanib – Placebo.
[4] - Treatment comparison of slopes was assessed through the treatment-by-time interaction coefficient. P-value was not adjusted for multiple comparisons. P-value .0001 is actually <.0001.

Primary: Annual rate of decline in Forced Vital Capacity - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Annual rate of decline in Forced Vital Capacity - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Annual rate of decline in Forced Vital Capacity in milliliter (mL) per year in subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only is based on a random coefficient regression with fixed effects for treatment, baseline FVC [mL], and including treatment−by−time and baseline−by−time interactions. Within−subject errors are modelled by an unstructured variance−covariance matrix.

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Primary

End point timeframe:

Baseline, 2, 4, 6, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[5]	206[6]		
Units: Milliliter per year				
least squares mean (confidence interval 95%)	-82.87 (-123.73 to	-211.07 (-251.38 to		

	-42.02)	-170.77)

Notes:

[5] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[6] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The decrease in FVC was assumed to be linear within each participant over 52 weeks. The intercepts and slopes were assumed to be
normally distributed with unstructured covariance matrix. The within participant error was assumed to be independent and normally
distributed with mean 0 and a common variance. The Kenward-Roger approximation was used to estimate denominator degrees of
freedom and adjust standard errors (SEs).

Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Difference of adjusted annual rates
Point estimate	128.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	70.81
upper limit	185.59
Variability estimate	Standard error of the mean
Dispersion value	29.17

Notes:

[7] - Fixed effects: Treatment, baseline FVC (mL), treatment-by-time, baseline-by-time interactions. Random effects: time, intercept. Difference of adjusted annual rates of decline was calculated as Nintedanib – Placebo.

[8] - Treatment comparison of slopes was assessed through the treatment-by-time interaction coefficient. P-value was not adjusted for multiple comparisons. P-value .0001 is actually <.0001.

Secondary: Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) Total score at week 52 - Overall population

End point title	Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) Total score at week 52 - Overall population

End point description:

King's Brief Interstitial Lung Disease questionnaire (K-BILD) consists of 15 items and 3 domains: breathlessness and activities, psychological, chest symptoms ranging from 0-100, with 100 representing the best health status. If missing items were >50% per domain, the domain score was set to missing. If any of the domain scores were missing, the total score was set to missing. Absolute change from baseline at week 52 was based on a Mixed Model Repeated Measures (MMRM), with fixed effects for baseline K-BILD Total score, HRCT fibrotic pattern, visit, treatment-by-visit interaction, baseline-by-visit interactions and random effect for subject. Visit was the repeated measure. Within-subject errors were modelled by unstructured variance-covariance matrix.

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[9]	330[10]		
Units: Unit on scale				
least squares mean (confidence interval 95%)	0.55 (-0.62 to 1.72)	-0.79 (-1.94 to 0.37)		

Notes:

[9] - Overall Population

[10] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	662
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.1115
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	2.98
Variability estimate	Standard error of the mean
Dispersion value	0.84

Notes:

[11] - No formal hypotheses were tested.
Fixed effects: baseline K-BILD Total score, visit, treatment−by−visit and baseline−by−visit interactions, random effect: participant.
Adjusted mean difference was calculated as Nintedanib – Placebo.

Secondary: Absolute change from baseline in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total score at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Absolute change from baseline in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total score at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

King's Brief Interstitial Lung Disease questionnaire (K-BILD) consists of 15 items and 3 domains: breathlessness, activities, psychological, chest symptoms ranging from 0-100, with 100 representing best health status. If missing items were >50% per domain, the domain score was set to missing. If any of the domain scores were missing, the total score was set to missing. Absolute change from baseline at week 52 was based on a Mixed Model Repeated Measures (MMRM), with fixed effects for baseline K-BILD Total score, HRCT fibrotic pattern, visit, treatment-by-visit interaction, baseline-by-visit interactions and random effect for subject and visit as repeated measure. Within-subject errors were modelled by unstructured variance-covariance matrix.

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[12]	205[13]		
Units: Unit on scale				
least squares mean (confidence interval 95%)	0.75 (-0.82 to 2.31)	-0.78 (-2.34 to 0.78)		

Notes:

[12] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[13] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 4
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1747
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Adjusted mean difference
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	3.74
Variability estimate	Standard error of the mean
Dispersion value	1.12

Secondary: Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over 52 weeks - Overall population

End point title	Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over 52 weeks - Overall population

End point description:

Time to first acute ILD exacerbation or death over 52 weeks was defined as time to first acute ILD exacerbation or death due to any cause within the first 52 weeks and was computed as earliest of date of first documented acute ILD exacerbation or death – date of first drug intake + 1. Subjects alive who did not experience any ILD exacerbation event or with unknown status within the first 52 weeks were censored. The value '99999' stands for non-calculable because the 25 percentile was not reached.

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first drug intake until date of first acute ILD exacerbation or date of death or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[14]	331[15]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[14] - Overall Population

[15] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3948
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.34

Secondary: Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over 52 weeks – Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Time to first acute Interstitial Lung Disease (ILD) exacerbation or death over 52 weeks – Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Time to first acute ILD exacerbation or death over 52 weeks was defined as time to first acute ILD exacerbation or death due to any cause within the first 52 weeks and was computed as earliest of date of first documented acute ILD exacerbation or death – date of first drug intake + 1. Subjects alive who did not experience any ILD exacerbation event or with unknown status within the first 52 weeks were censored. The value '99999' stands for non-calculable because the 25 percentile was not reached.

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first drug intake until date of first acute ILD exacerbation or date of death or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[16]	206[17]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[16] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[17] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 6
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1985
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.24

Secondary: Time to death over 52 weeks - Overall population

End point title	Time to death over 52 weeks - Overall population

End point description:

Time to death over 52 weeks defined as the time from date of first drug intake until date of death from any cause for subjects with known date of death (from any cause) within the first 52 weeks. Subjects with no event (death from any cause) or unknown status within the first 52 weeks were censored. The value '99999' stands for non-calculable because the 25 percentile was not reached.

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first drug intake until date of death or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[18]	331[19]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[18] - Overall Population

[19] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 7
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8544
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.86

Secondary: Time to death over 52 weeks - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Time to death over 52 weeks - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Time to death over 52 weeks defined as the time from date of first drug intake until date of death from any cause for subjects with known date of death (from any cause) within the first 52 weeks. Subjects with no event (death from any cause) or unknown status within the first 52 weeks were censored. The value '99999' stands for non-calculable because the 25 percentile was not reached.

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first drug intake until date of death or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[20]	206[21]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[20] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[21] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 8
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3291
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.47

Secondary: Time to death due to respiratory cause over 52 weeks - Overall population

End point title	Time to death due to respiratory cause over 52 weeks - Overall population

End point description:

Time to death due to respiratory cause over 52 weeks is defined as the time from date of first drug intake until date of death attributed to respiratory causes (determined by an independent Adjudication Committee) for subjects with known date of death (from respiratory causes) within the first 52 weeks. Subjects with no event (death from respiratory causes) or unknown status within the first 52 weeks were censored. As less than 4.95% of the total of subjects in the analysis population experienced an event, only descriptive statistics were performed, as pre-specified. The value '99999' stands for non-calculable because the 25 percentile was not reached. No statistical analysis provided for Time to death due to respiratory cause over 52 weeks.

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From date of first trial drug intake up to date of death from respiratory causes or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[22]	331[23]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[22] - Overall population

[23] - Overall population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to death due to respiratory cause over 52 weeks - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Time to death due to respiratory cause over 52 weeks - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Time to death due to respiratory cause over 52 weeks is defined as the time from date of first drug intake until date of death attributed to respiratory causes (determined by an independent Adjudication Committee) for subjects with known date of death (from respiratory causes) within the first 52 weeks. Subjects with no event (death from respiratory causes) or unknown status within the first 52 weeks were censored. As less than 4.95% of the total of subjects in the analysis population experienced an event, only descriptive statistics were performed, as pre-specified. The value '99999' stands for non-calculable because the 25 percentile was not reached. No statistical analysis provided for Time to death due to respiratory cause over 52.

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From date of first trial drug intake up to date of death from respiratory causes or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[24]	206[25]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[24] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[25] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression or death over 52 weeks - Overall population

End point title	Time to progression or death over 52 weeks - Overall population

End point description:

Time to progression or death over 52 weeks is as the time from date of first drug intake to date of progression, or date of death (from any cause) if a subject died earlier. Subjects with no event (progression or death from any cause) or unknown status were censored. Date of progression defined as the date when ≥ 10% of absolute decline in FVC percent predicted compared to baseline occurred for the first time. Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) forcibly exhaled from the lungs after taking the deepest breath possible. Predicted normal values of FVC were calculated according to the Global Lung Initiative. FVC percent predicted (FVC % pred) is the FVC divided by its predicted value in percent. The value '99999' stands for non-calculable because the 50 percentile was not reached.

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first drug intake until date of progression or date of death or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[26]	331[27]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (367 to 99999)	99999 (269 to 99999)		

Notes:

[26] - Overall Population

[27] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 9
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0017
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.85

Secondary: Time to progression or death over 52 weeks - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Time to progression or death over 52 weeks - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Time to progression or death over 52 weeks defined as time from date of first drug intake to date of

progression, or date of death (from any cause) if a participant died earlier. Subjects with no event (progression or death from any cause) or unknown status were censored. Date of progression defined as the date when ≥ 10% of absolute decline in FVC percent predicted compared to baseline occurred for the first time. FVC is the volume of air (measured in milliliter) forcibly exhaled from the lungs after taking the deepest breath possible. Predicted normal values of FVC were calculated according to the Global Lung Initiative. FVC percent predicted (FVC % pred) is the FVC divided by its predicted value in percent. The value '99999' stands for non-calculable because the 50 percentile was not reached. Subjects with HRCT fibrotic pattern= UIP-like fibrotic pattern (HRCT=UIP FP) only: All randomised subjects with HRCT=UIP FP only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

From first drug intake until date of progression or date of death or last contact date, up to 372 days

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[28]	206[29]		
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (365 to 99999)	99999 (254 to 99999)		

Notes:

[28] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[29] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 10
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0081
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.89

Secondary: Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 10 percent at week 52 - Overall population

End point title	Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 10 percent at week 52 - Overall population

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Predicted normal values of FVC were calculated according to the Global Lung Initiative. FVC percent predicted (FVC % pred) is the FVC divided by its predicted value in percent. Subjects with relative decline from baseline in FVC % pred greater than 10%

at week 52 were those subjects with a negative relative change from baseline in FVC % pred at week 52 the absolute value of which being greater than 10% and those subjects with missing data (worst case analysis).

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline and up to 52 weeks after first drug intake

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[30]	331[31]		
Units: Percentage of subjects				
number (not applicable)	40.7	48.9		

Notes:

[30] - Overall Population

[31] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 11
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.96

Secondary: Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 10 percent at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 10 percent at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Predicted normal values of FVC were calculated according to the Global Lung Initiative. FVC percent predicted (FVC % pred) is the FVC divided by its predicted value in percent. Subjects with relative decline from baseline in FVC % pred greater than 10% at week 52 were those subjects with a negative relative change from baseline in FVC % pred at week 52 the absolute value of which being greater than 10% and those subjects with missing data (worst case analysis).

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline and up to 52 weeks after first drug intake

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[32]	206[33]		
Units: Percentage of participants				
number (not applicable)	41.3	52.4		

Notes:

[32] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[33] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 12
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.94

Secondary: Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 5 percent at week 52 - Overall population

End point title	Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 5 percent at week 52 - Overall population

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Predicted normal values of FVC were calculated according to the Global Lung Initiative. FVC percent predicted (FVC % pred) is the FVC divided by its predicted value in percent. Subjects with relative decline from baseline in FVC % pred greater than 5% at week 52 were those subjects with a negative relative change from baseline in FVC % pred at week 52 the absolute value of which being greater than 5% and those subjects with missing data (worst case analysis).

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline and up to 52 weeks after first drug intake

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[34]	331[35]		
Units: Percentage of subjects				
number (not applicable)	52.4	68.6		

Notes:

[34] - Overall population

[35] - Overall population

Statistical analyses

Statistical analysis title	Statistical Analysis 13
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.68

Secondary: Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 5 percent at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Percentage of subjects with a relative decline from baseline in FVC percent predicted of more than 5 percent at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Forced Vital Capacity (FVC) is the volume of air (measured in milliliter) which can be forcibly exhaled from the lungs after taking the deepest breath possible. Predicted normal values of FVC were calculated according to the Global Lung Initiative. FVC percent predicted (FVC % pred) is the FVC divided by its predicted value in percent. Subjects with relative decline from baseline in FVC % pred greater than 5% at week 52 were those subjects with a negative relative change from baseline in FVC % pred at week 52 the absolute value of which being greater than 5% and those subjects with missing data (worst case analysis).

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline and up to 52 weeks after first drug intake

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206[36]	206[37]		
Units: Percentage of subjects				
number (not applicable)	52.4	70.4		

Notes:

[36] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[37] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 14
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Logistic
Parameter estimate	Adjusted Odds Ratio
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.69

Secondary: Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnea domain score at week 52 - Overall population

End point title	Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnea domain score at week 52 - Overall population

End point description:

Living with Pulmonary Fibrosis (L-PF) questionnaire with 44 items in two modules: Symptoms (23 items with three domains: dyspnea, cough and fatigue and a total score) and Impacts (21 items as a single score). L-PF Symptoms dyspnea domain score (dyspnea score) ranges from 0-100, with higher scores indicating greater impairment. A score was set to missing if ≥50 % items were missing. Absolute change from baseline at week 52 based on a Mixed Model Repeated Measures, with fixed effects for baseline dyspnea score, HRCT fibrotic pattern, visit, treatment-by-visit interaction, baseline dyspnea score-by-visit interaction and random effect for subject, visit as repeated measure. Adjusted mean is based on all analysed subjects in the model (not only subjects with a baseline and measurement at week 52).

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329[38]	323[39]		
Units: Unit on scale				
least squares mean (confidence interval 95%)	4.28 (2.43 to 6.14)	7.81 (5.97 to 9.66)		

Notes:

[38] - Overall Population

[39] - Overall Population

Statistical analyses

Statistical analysis title	Statistical Analysis 15
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	652
Analysis specification	Pre-specified
Analysis type	
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-3.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.14
upper limit	-0.92
Variability estimate	Standard error of the mean
Dispersion value	1.33

Secondary: Absolute change from baseline in L-PF Symptoms dyspnea domain score at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Absolute change from baseline in L-PF Symptoms dyspnea domain score at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Living with Pulmonary Fibrosis (L-PF) questionnaire with 44 items in two modules: Symptoms (23 items with three domains: dyspnea, cough and fatigue and a total score) and Impacts (21 items as a single score). L-PF Symptoms dyspnea domain score (dyspnea score) ranges from 0-100, with higher scores indicating greater impairment. A score was set to missing if ≥50 % items were missing. Absolute change from baseline at week 52 based on a Mixed Model Repeated Measures, with fixed effects for baseline dyspnea score, visit, treatment-by-visit interaction, baseline dyspnea score treatment-by-visit interaction and random effect for subject, visit as repeated measure. Adjusted mean is based on all analysed subjects in the model (not only subjects with a baseline and measurement at week 52).

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[40]	201[41]		
Units: Unit on scale				
least squares mean (confidence interval 95%)	4.14 (1.81 to 6.47)	8.32 (5.99 to 10.66)		

Notes:

[40] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[41] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 16
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.48
upper limit	-0.88
Variability estimate	Standard error of the mean
Dispersion value	1.68

Secondary: Absolute change from baseline in L-PF Symptoms cough domain score at week 52 - Overall population

End point title	Absolute change from baseline in L-PF Symptoms cough domain score at week 52 - Overall population

End point description:

Living with Pulmonary Fibrosis (L-PF) questionnaire with 44 items in two modules: Symptoms (23 items with three domains: dyspnea, cough and fatigue and a total score) and Impacts (21 items as a single score). L-PF Symptoms cough domain score (cough score) ranges from 0-100, higher scores indicating greater impairment. A score was set to missing if ≥50 % items were missing. Absolute change from baseline at week 52 based on a Mixed Model Repeated Measures, with fixed effects for baseline cough score, HRCT fibrotic pattern, visit, treatment-by-visit interaction, baseline cough score-by-visit interaction and random effect for subject, visit as repeated measure. Adjusted mean is based on all analysed subjects in the model (not only subjects with a baseline and measurement at week 52).

Overall Population: All randomised subjects in the overall population who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327[42]	320[43]		
Units: Unit on scale				
least squares mean (confidence interval 95%)	-1.84 (-4.36 to 0.69)	4.25 (1.74 to 6.76)		

Notes:

[42] - Overall population

[43] - Overall population

Statistical analyses

Statistical analysis title	Statistical Analysis 17
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	647
Analysis specification	Pre-specified
Analysis type	
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-6.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.65
upper limit	-2.53
Variability estimate	Standard error of the mean
Dispersion value	1.81

Secondary: Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point title	Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score at week 52 - Subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only

End point description:

Living with Pulmonary Fibrosis (L-PF) with 44 items in two modules: Symptoms (23 items with three domains: dyspnea, cough and fatigue and a total score) and Impacts (21 items as a single score). L-PF Symptoms cough domain score (cough score) ranges from 0-100, higher scores indicating greater impairment. A score was set to missing if ≥50 % items were missing. Absolute change from baseline at week 52 based on a Mixed Model Repeated Measures, with fixed effects for baseline cough score, visit, treatment-by-visit interaction, baseline cough score-by-visit interaction and random effect for subject, visit as repeated measure. Adjusted mean is based on all analysed subjects in the model (not only subjects with a baseline and measurement at week 52).

Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only: All randomised subjects with HRCT fibrotic pattern=UIP-like fibrotic pattern only who received at least 1 dose of trial medication.

End point type	Secondary

End point timeframe:

Baseline, 12, 24, 36, 52 weeks after first drug intake (planned post-baseline visits)

End point values	150 mg Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[44]	199[45]		
Units: Unit on scale				
least squares mean (confidence interval 95%)	-3.20 (-6.43 to 0.04)	4.09 (0.85 to 7.32)		

Notes:

[44] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

[45] - Subjects with HRCT fibrotic pattern = UIP-like fibrotic pattern only

Statistical analyses

Statistical analysis title	Statistical Analysis 18
Comparison groups	150 mg Nintedanib v Placebo
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	
Method	Mixed Model Repeated Measures
Parameter estimate	Adjusted mean difference
Point estimate	-7.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.86
upper limit	-2.71
Variability estimate	Standard error of the mean
Dispersion value	2.33

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment period plus 28 days (residual effect period), up to 836 days.
Time frame for All-Cause-Mortality: Treatment period plus Follow-up, up to 900 days.

Adverse event reporting additional description:

All participants who signed the informed consent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	150 mg Nintedanib

Reporting group description:

150 milligram (mg) Nintedanib as soft gelatine capsule, administered orally, twice daily (bid), with optional dose reduction to 100 mg bid to manage adverse events (AEs). Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, participants continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Reporting group title	Placebo

Reporting group description:

150 mg Nintedanib matching placebo, soft gelatine capsule, administered orally, bid, with optional dose reduction to 100 mg bid to manage AEs. Continuous daily dosing over a 52-week treatment period (Part A). After completion of the 52-week treatment period, participants continued on blinded treatment until the end of the trial or until a reason for treatment withdrawal was met (Part B).

Serious adverse events	150 mg Nintedanib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	147 / 332 (44.28%)	164 / 331 (49.55%)	
number of deaths (all causes)	36	45	
number of deaths resulting from adverse events	15	30	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 332 (0.60%)	4 / 331 (1.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder adenocarcinoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung squamous cell carcinoma metastatic			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Salivary gland adenoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Arteritis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 332 (0.60%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic vascular disorder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vasculitis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Discomfort			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	16 / 332 (4.82%)	7 / 331 (2.11%)	
occurrences causally related to treatment / all	0 / 19	0 / 8	
deaths causally related to treatment / all	0 / 5	0 / 2	

Asthma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 332 (0.30%)	6 / 331 (1.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 332 (1.81%)	13 / 331 (3.93%)	
occurrences causally related to treatment / all	0 / 6	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eosinophilic pneumonia chronic			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity pneumonitis			
subjects affected / exposed	2 / 332 (0.60%)	4 / 331 (1.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	3 / 332 (0.90%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic interstitial pneumonia			

subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	19 / 332 (5.72%)	45 / 331 (13.60%)	
occurrences causally related to treatment / all	0 / 22	1 / 53	
deaths causally related to treatment / all	0 / 2	0 / 7	
Lung disorder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	6 / 332 (1.81%)	6 / 331 (1.81%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 332 (0.30%)	5 / 331 (1.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	7 / 332 (2.11%)	5 / 331 (1.51%)	
occurrences causally related to treatment / all	0 / 7	1 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	5 / 332 (1.51%)	9 / 331 (2.72%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 332 (0.00%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
subjects affected / exposed	11 / 332 (3.31%)	10 / 331 (3.02%)	
occurrences causally related to treatment / all	0 / 15	0 / 11	
deaths causally related to treatment / all	0 / 4	0 / 5	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram Q wave abnormal			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotavirus test positive			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery restenosis			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 332 (0.90%)	4 / 331 (1.21%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 332 (0.30%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 332 (0.90%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 332 (0.60%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 332 (1.51%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 332 (0.30%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 332 (0.90%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 332 (0.30%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic right ventricular failure			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale acute			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 332 (0.30%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Long QT syndrome			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 332 (0.60%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic anterior motion of mitral valve			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokinesia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 332 (0.00%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mixed deafness			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 332 (0.30%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			

subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vascular thrombosis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 332 (0.90%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 332 (0.90%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 332 (0.00%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	6 / 332 (1.81%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	6 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver injury			
subjects affected / exposed	3 / 332 (0.90%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma gangrenosum			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 332 (0.90%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Connective tissue disorder			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Groin pain			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyositis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sjogren's syndrome			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic scleroderma			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Winged scapula			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 332 (1.20%)	5 / 331 (1.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 332 (0.60%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 332 (0.30%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			

subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 332 (0.30%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	4 / 332 (1.20%)	4 / 331 (1.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leishmaniasis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 332 (0.30%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	3 / 332 (0.90%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	24 / 332 (7.23%)	16 / 331 (4.83%)	
occurrences causally related to treatment / all	0 / 27	0 / 19	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pneumonia bacterial			
subjects affected / exposed	1 / 332 (0.30%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			

subjects affected / exposed	0 / 332 (0.00%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 332 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 332 (0.90%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 332 (0.30%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	2 / 332 (0.60%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 332 (0.60%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 332 (0.30%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 332 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	150 mg Nintedanib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	308 / 332 (92.77%)	266 / 331 (80.36%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	47 / 332 (14.16%)	12 / 331 (3.63%)	
occurrences (all)	53	17	
Aspartate aminotransferase increased			
subjects affected / exposed	41 / 332 (12.35%)	12 / 331 (3.63%)	
occurrences (all)	49	16	
Gamma-glutamyltransferase increased			
subjects affected / exposed	22 / 332 (6.63%)	6 / 331 (1.81%)	
occurrences (all)	29	6	
Weight decreased			
subjects affected / exposed	49 / 332 (14.76%)	18 / 331 (5.44%)	
occurrences (all)	53	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 332 (5.72%)	15 / 331 (4.53%)	
occurrences (all)	34	16	
Headache			
subjects affected / exposed	37 / 332 (11.14%)	27 / 331 (8.16%)	
occurrences (all)	52	37	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 332 (5.42%)	14 / 331 (4.23%)	
occurrences (all)	20	17	
Chest pain			
subjects affected / exposed	17 / 332 (5.12%)	14 / 331 (4.23%)	
occurrences (all)	21	14	
Fatigue			
subjects affected / exposed	34 / 332 (10.24%)	21 / 331 (6.34%)	
occurrences (all)	38	25	
Oedema peripheral			

subjects affected / exposed	18 / 332 (5.42%)	22 / 331 (6.65%)	
occurrences (all)	18	28	
Pyrexia			
subjects affected / exposed	17 / 332 (5.12%)	18 / 331 (5.44%)	
occurrences (all)	19	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	34 / 332 (10.24%)	9 / 331 (2.72%)	
occurrences (all)	42	10	
Abdominal pain upper			
subjects affected / exposed	33 / 332 (9.94%)	6 / 331 (1.81%)	
occurrences (all)	46	6	
Constipation			
subjects affected / exposed	25 / 332 (7.53%)	32 / 331 (9.67%)	
occurrences (all)	29	36	
Diarrhoea			
subjects affected / exposed	239 / 332 (71.99%)	85 / 331 (25.68%)	
occurrences (all)	577	115	
Nausea			
subjects affected / exposed	100 / 332 (30.12%)	33 / 331 (9.97%)	
occurrences (all)	173	45	
Vomiting			
subjects affected / exposed	64 / 332 (19.28%)	16 / 331 (4.83%)	
occurrences (all)	129	20	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	19 / 332 (5.72%)	3 / 331 (0.91%)	
occurrences (all)	27	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	40 / 332 (12.05%)	50 / 331 (15.11%)	
occurrences (all)	48	66	
Dyspnoea			
subjects affected / exposed	49 / 332 (14.76%)	46 / 331 (13.90%)	
occurrences (all)	54	56	
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	12 / 332 (3.61%)	18 / 331 (5.44%)	
occurrences (all)	14	19	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 332 (5.42%)	18 / 331 (5.44%)	
occurrences (all)	19	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 332 (3.61%)	23 / 331 (6.95%)	
occurrences (all)	13	24	
Back pain			
subjects affected / exposed	28 / 332 (8.43%)	26 / 331 (7.85%)	
occurrences (all)	31	34	
Infections and infestations			
Bronchitis			
subjects affected / exposed	44 / 332 (13.25%)	62 / 331 (18.73%)	
occurrences (all)	62	86	
Nasopharyngitis			
subjects affected / exposed	54 / 332 (16.27%)	48 / 331 (14.50%)	
occurrences (all)	72	68	
Respiratory tract infection			
subjects affected / exposed	18 / 332 (5.42%)	12 / 331 (3.63%)	
occurrences (all)	28	19	
Upper respiratory tract infection			
subjects affected / exposed	26 / 332 (7.83%)	25 / 331 (7.55%)	
occurrences (all)	31	29	
Urinary tract infection			
subjects affected / exposed	22 / 332 (6.63%)	20 / 331 (6.04%)	
occurrences (all)	29	22	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	54 / 332 (16.27%)	22 / 331 (6.65%)	
occurrences (all)	69	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2016	To address a recommendation by the FDA, the primary analysis of the primary endpoint was also planned to be performed in the complementary population of patients with other High Resolution Computed Tomography (HRCT) fibrotic patterns; Serum banking was changed from mandatory to optional to ensure that the trial could be conducted according to regulatory and ethical requirements in the participating countries; Flow chart Part B was updated to ensure that Electrocardiogram (ECG) was also performed at end of trial part B (EOTB); Scoring instructions for Living with Pulmonary Fibrosis (L-PF) domains were updated; Information was added to adapt informed consent handling for specific regulatory requirements in Japan;
08 June 2018	Following main changes were introduced: End of trial (EOT) and roll over in the open-label extension trial: After BI communicated end of the trial, EOTB Visit was performed in all ongoing patients. Patients receiving trial medication until end of Part B could be eligible for open-label treatment with nintedanib in a separate trial. Trial 1199.247 was planned to last until all patients completed EOTB Visit and Follow-up Visit as applicable; End of trial part A (EOTA) was done in cases of premature trial medication discontinuation during Part A of the trial with a Follow-up Visit 4 weeks later. A scheduled visit (V3-V9) could be skipped if EOTA or Follow-up Visit occurred within 4 weeks prior to scheduled visits; In case of premature discontinuation of trial medication during Part B, EOTB was done as soon as possible after last drug intake and a Follow-up Visit was to be completed 4 weeks after EOTB. A scheduled visit could be skipped if EOTB or Follow-up Visit occurred within 4 weeks prior to scheduled visits. For patients completing the trial regularly, EOTB was scheduled after BI's communication of the end of the trial. For patients not rolling over in the separate open-label trial, a Follow-up Visit was completed 4 weeks after EOTB. The specific time window for EOTB was removed, time intervals for Visits X and Xa corrected, and the need for Interactive Response Technology (IRT) call included; All adverse events (AE)s (non-serious and serious), all AE of special interest (AESIs) were collected after the EOT, including the residual effect period until the individual patient's end of trial; Additional AE analyses were specified to take the half-life of the trial drug into account: AEs that occurred between start of treatment and up to 7 days after date of last dose of trial medication were analysed in addition; Details were added regarding drug induced liver injury (DILI) handling: Potential DILI cases were defined as AESIs and a DILI checklist had to be completed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported