Clinical trial results:
A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)

Summary

EudraCT number	2010-024251-87
Trial protocol	DE GB BE IE CZ IT
Global end of trial date	09 October 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	1199.32

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01335464
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein , Germany,
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800243 0127, 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	21 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2013
Global end of trial reached?	Yes
Global end of trial date	09 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate a reduction of lung function decline, as measured by a change of the yearly rate of decline of forced vital capacity (FVC).

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 patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 41
Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	China: 68
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	France: 95
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	India: 15
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Italy: 105
Country: Number of subjects enrolled	Japan: 72
Country: Number of subjects enrolled	United Kingdom: 61
Country: Number of subjects enrolled	United States: 112
Worldwide total number of subjects	718
EEA total number of subjects	385

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)	260
From 65 to 84 years	452
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended one specialist site which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Oral administration of placebo matching nintedanib soft gelatine capsules

Two patients were randomised to the placebo arm, however those two patients were not treated. Consequently, number of subjects that started is 206 but only 204 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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:

Oral administration of placebo matching nintedanib soft gelatine capsules twice daily (bid)

Arm title	Nintedanib 150mg

Arm description:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).
Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

Arm type	Experimental
Investigational medicinal product name	Nintedanib 150mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).
In case of lack of tolerability of Nintedanib 150mg bid, the dose could have been reduced to 100mg bid.

Number of subjects in period 1[1]	Placebo	Nintedanib 150mg
Started	204	309
Completed	174	260
Not completed	30	49
Adverse event, serious fatal	10	9
Consent withdrawn by subject	12	23
Reason other than those stated above	1	1
Adverse event, non-fatal	5	16
Protocol deviation	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 of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Oral administration of placebo matching nintedanib soft gelatine capsules

Two patients were randomised to the placebo arm, however those two patients were not treated. Consequently, number of subjects that started is 206 but only 204 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Nintedanib 150mg

Reporting group description:

Oral administration of soft gelatine capsules of nintedanib 150mg twice daily (bid).
Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

Reporting group values	Placebo	Nintedanib 150mg	Total
Number of subjects	204	309	513
Age categorical Units: Subjects			

Age continuous			
Treated set (TS): The TS consisted of randomised patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment			
Units: years			
arithmetic mean	66.9	66.9	
standard deviation	± 8.2	± 8.4	-
Gender categorical			
Treated set (TS): The TS consisted of randomised patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment			
Units: Subjects			
Female	41	58	99
Male	163	251	414

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Oral administration of placebo matching nintedanib soft gelatine capsules

Two patients were randomised to the placebo arm, however those two patients were not treated. Consequently, number of subjects that started is 206 but only 204 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Nintedanib 150mg

Reporting group description:

Oral administration of soft gelatine capsules of nintedanib 150mg
twice daily (bid).
Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

Primary: Annual Rate of Decline in Forced Vital Capacity (FVC) Over 52 Weeks

End point title	Annual Rate of Decline in Forced Vital Capacity (FVC) Over 52 Weeks

End point description:

Forced vital capacity (FVC) is the total amount of air exhaled during the lung function test.
The reported mean represents the adjusted rate.

End point type	Primary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[1]	309[2]		
Units: mL/year				
arithmetic mean (standard error)	-239.91 (± 18.709)	-114.65 (± 15.327)		

Notes:

[1] - TS (Only patients with observed cases (OC) values were analysed)

[2] - TS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Random coefficient regression with fixed effects for treatment, gender, age, height and random effect of patient specific intercept and time. A hierarchical procedure was used in order to demonstrate the superiority of nintedanib over placebo for the primary and two key secondary endpoints. The consecutive steps of the hierarchy were only considered if the previous step was significant at the one-sided 2.5% level and the results were in favour of nintedanib.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Random coefficient regression
Parameter estimate	Mean difference (final values)
Point estimate	125.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	77.68
upper limit	172.84
Variability estimate	Standard error of the mean
Dispersion value	24.209

Notes:

[3] - Nintedanib 150 mg bid versus Placebo
The Roger-Kenward approximation was used to estimate denominators degrees of freedom.

Within-patient errors are modeled by an Unstructured variance-covariance matrix.
Inter-individual variability is modelled by a Variance-components variance-covariance matrix.

Secondary: Change From Baseline in Saint George's Respiratory Questionnaire (SGRQ) Total Score at 52 Weeks

End point title	Change From Baseline in Saint George's Respiratory Questionnaire (SGRQ) Total Score at 52 Weeks

End point description:

This is a key secondary endpoint.
SGRQ is a health-related quality of life questionnaire divided into 3 components : symptoms, activity and impact.
The total score (summed weights) can range from 0 to 100 with a lower score denoting a better health status.
Means provided are the adjusted means based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

End point type	Secondary

End point timeframe:

baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[4]	289[5]		
Units: points on a scale				
arithmetic mean (standard error)	4.39 (± 0.96)	4.34 (± 0.799)		

Notes:

[4] - TS (Only patients with observed cases (OC) values were analysed)

[5] - TS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SGRQ Total score, baseline SGRQ Total score by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.9657
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	1.248

Notes:

[6] - Nintedanib 150 mg bid versus Placebo.
Within-patient errors were modelled by compound symmetry covariance matrix.

Secondary: Absolute Change From Baseline in FVC Over 52 weeks

End point title	Absolute Change From Baseline in FVC Over 52 weeks

End point description:

Absolute Change From Baseline in Forced Vital Capacity (FVC) Over 52 weeks.
Means provided are the adjusted means. Adjusted mean is based on all analysed patients in the model (not only patients with a change from baseline to week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[7]	307[8]		
Units: mL				
arithmetic mean (standard error)	-205 (± 16.544)	-95.07 (± 14.375)		

Notes:

[7] - TS (Only patients with observed cases (OC) values were analysed)

[8] - TS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC, baseline FVC-by visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	109.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.27
upper limit	148.59
Variability estimate	Standard error of the mean
Dispersion value	19.708

Notes:

[9] - Nintedanib 150 mg bid versus Placebo
Within-patient errors are modelled by compound symmetry covariance matrix

Secondary: Absolute Change From Baseline in FVC (% predicted) over 52 weeks

End point title	Absolute Change From Baseline in FVC (% predicted) over 52 weeks

End point description:

Means provided are the adjusted means. Adjusted mean is based on all analysed patients in the model (not only patients with a change from baseline to week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[10]	307[11]		
Units: %predicted				
arithmetic mean (standard error)	-5.98 (± 0.474)	-2.76 (± 0.408)		

Notes:

[10] - TS (Only patients with observed cases (OC) values were analysed)

[11] - TS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC [%predicted], baseline FVC [%predicted]-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.11
upper limit	4.33
Variability estimate	Standard error of the mean
Dispersion value	0.564

Notes:

[12] - Nintedanib 150 mg bid versus Placebo.
Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Absolute Categorical Change of FVC (% Predicted) - 5% Threshold

End point title	Absolute Categorical Change of FVC (% Predicted) - 5% Threshold

End point description:

Absolute categorical change of FVC (% predicted) by categories at 52 weeks - 5% threshold (decrease by >5%, increase by >5%, and change within ≤5%).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165[13]	250[14]		
Units: percentage of participants				
number (not applicable)				
Decrease > 5%	52.7	34.8		
Change within ≤ 5%	41.2	54		
Increase > 5%	6.1	11.2		

Notes:

[13] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

[14] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Categorical Change of FVC (% Predicted) - 10% Threshold

End point title	Absolute Categorical Change of FVC (% Predicted) - 10% Threshold

End point description:

Absolute categorical change of FVC (% predicted) by categories at 52 weeks - 10% threshold (decrease by > 10%, increase by >10%, and change

within ≤10%.

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165[15]	250[16]		
Units: percentage of participants				
number (not applicable)				
Decrease > 10%	29.7	12.8		
Change within ≤10%	69.1	84.4		
Increase > 10%	1.2	2.8		

Notes:

[15] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

[16] - Treated Set (for patients with change from baseline in FVC (%predicted) at Week 52)

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of SGRQ Responders at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Proportion of SGRQ Responders at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

Proportion of SGRQ Responders at 52 Weeks.
Responders defined as <= -4 points change in change from baseline in SGRQ total score at 52 weeks.

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[17]	309[18]		
Units: percentage of participants				
number (confidence interval 95%)	24.02 (18.67 to 30.33)	20.39 (16.27 to 25.23)		

Notes:

[17] - Treated Set (Only patients with observed cases (OC) values were analysed)

[18] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:	
Logistic regression with terms treatment, baseline SGRQ total score	
Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.4298
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.29

Notes:

[19] - Nintedanib 150 mg bid versus Placebo

Secondary: Change From Baseline in SGRQ Symptom Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in SGRQ Symptom Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

SGRQ Symptom score is a sub-component of SGRQ total score and is concerned with the effect of respiratory symptoms, their frequency and severity. This score calculated as summed weights ranges from 0 to 100 with lower score denoting a better symptom-related quality of life.
Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[20]	300[21]		
Units: points on a scale				
arithmetic mean (standard error)	3.89 (± 1.351)	1.56 (± 1.104)		

Notes:

[20] - Treated Set (Only patients with observed cases (OC) values were analysed)

[21] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit treatment-by-visit, baseline SGRQ Symptoms component, baseline SGRQ Symptoms component-by-visit and random effect for patient.

Comparison groups	Nintedanib 150mg v Placebo

Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.1832
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	1.744

Notes:

[22] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Change From Baseline in SGRQ Impact Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in SGRQ Impact Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

SGRQ Impact score is a sub-component of SGRQ total score and covers a range of aspects concerned with social functioning and psychological
disturbances resulting from airway disease. This score calculated as summed weights ranges from 0 to 100 with lower score denoting a better
impact-related quality of life.

End point type	Secondary

End point timeframe:

baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[23]	291[24]		
Units: points on a scale				
arithmetic mean (standard error)	4.01 (± 1.113)	4.87 (± 0.923)		

Notes:

[23] - Treated Set (Only patients with observed cases (OC) values were analysed)

[24] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SGRQ impact component, baseline SGRQ Impact component-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.551
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	1.446

Notes:

[25] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix

Secondary: Change From Baseline in SGRQ Activity Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in SGRQ Activity Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

SGRQ Activity score is a sub-component of SGRQ total score and concerned with activities that cause or are limited by breathlessness. This score calculated as summed weights ranges from 0 to 100 with lower score denoting a better activity-related quality of life. Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

End point type	Secondary

End point timeframe:

baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[26]	295[27]		
Units: points on scale				
arithmetic mean (standard error)	5.81 (± 1.103)	4.62 (± 0.906)		

Notes:

[26] - Treated Set (Only patients with observed cases (OC) values were analysed)

[27] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SGRQ Activities component, baseline SGRQ Activities component-by-visit and random effect for patient

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.4049
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.99
upper limit	1.61
Variability estimate	Standard error of the mean
Dispersion value	1.427

Notes:

[28] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Change From Baseline in Idiopathic Pulmonary Fibrosis (IPF) Specific Version of SGRQ (SGRQ-I) Total Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in Idiopathic Pulmonary Fibrosis (IPF) Specific Version of SGRQ (SGRQ-I) Total Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

SGRQ-I is the IPF specific version of SGRQ comprises of selected items from the SGRQ divided into three components, Symptoms, Activity and
Impact. Each component is scored separately. The weights for all items with a positive responses are summed and the weights from missed items are deducted from the maximum possible weight for the total score.
The total score is calculated by dividing the summed weights from positive items in the questionnaire by maximum possible weight for all items in the questionnaire. The total score can range from 0 to 100 with a lower score denoting a better health-related quality of life. Change from baseline is calculated as the difference between total score at week 52 and total score at baseline as measured by the scale.

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[29]	290[30]		
Units: points on a scale				
arithmetic mean (standard error)	5.08 (± 0.992)	4.3 (± 0.824)		

Notes:

[29] - Treated Set (Only patients with observed cases (OC) values were analysed)

[30] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit,

treatment-by-visit, baseline SGRQ-I Total score, baseline SGRQ-I Total score-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.5446
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	1.75
Variability estimate	Standard error of the mean
Dispersion value	1.289

Notes:

[31] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Change From Baseline in Shortness of Breath Questionnaire (SOBQ) at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in Shortness of Breath Questionnaire (SOBQ) at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

Shortness of Breath Questionnaire measures the shortness of breath. It comprises of 24 items. Each item is scored on a scale between 0-5 where 5 represents maximal breathlessness. The responses to all items are summed up to provide the overall score that can range from 0 (best outcome) to 120 (worst outcome).
Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

End point type	Secondary

End point timeframe:

baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178[32]	267[33]		
Units: points on a scale				
arithmetic mean (standard error)	7.61 (± 1.376)	6.73 (± 1.113)		

Notes:

[32] - Treated Set (Only patients with observed cases (OC) values were analysed)

[33] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline SOBQ score, baseline SOBQ score-by-visit and random

effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.6203
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.35
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	1.77

Notes:

[34] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Change From Baseline in Cough Symptoms Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in Cough Symptoms Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

The cough domains of the Cough and Sputum Assessment Questionnaire (CASAQ(CD)) assess the frequency and severity of cough and sputum and
their impact on everyday life. It contains 4 domains cough/sputum symptom and impact with each scale ranging from 0 to 100 with lower scores
indicating higher symptoms/impact levels (worst outcome).
Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[35]	302[36]		
Units: points on a scale				
arithmetic mean (standard error)	-0.52 (± 1.4)	-0.76 (± 1.136)		

Notes:

[35] - Treated Set (Only patients with observed cases (OC) values were analysed)

[36] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline CASA-Q Cough symptoms score, baseline CASA-Q Cough symptoms score-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.8942
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.78
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	1.803

Notes:

[37] - Nintedanib 150 mg versus Placebo.
Within- patient errors are modelled by compound symmetry covariance matrix.

Secondary: Change From Baseline in Cough Impact Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in Cough Impact Score of the Cough and Sputum Assessment Questionnaire (CASA-Q) Score at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

The cough domains of the Cough and Sputum Assessment Questionnaire (CASA-Q) assess the frequency and severity of cough and sputum and their impact on everyday life. It contains 4 domains cough/sputum symptom and impact with each scale ranging from 0 to 100 with lower scores indicating higher symptoms/impact levels (worst outcome).
Means presented are the adjusted means and are based on all analyzed patients in the model (not only patients with a baseline and measurement at week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202[38]	302[39]		
Units: points on a scale				
arithmetic mean (standard error)	-4 (± 1.24)	-2.36 (± 1.006)		

Notes:

[38] - Treated Set (Only patients with observed cases (OC) values were analysed)

[39] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, treatment-by-visit, baseline CASA-Q Cough impact score, baseline CASA-Q Cough impact score-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.3042
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	4.77
Variability estimate	Standard error of the mean
Dispersion value	1.596

Notes:

[40] - Nintedanib 150 mg versus Placebo.
Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Proportion of Patient’s Global Impression of Change (PGI-C) Responders at 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Proportion of Patient’s Global Impression of Change (PGI-C) Responders at 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

Proportion of Patient's Global Impression of Change (PGI-C) responders at 52 weeks. Responders are defined as 'Very much better'/ 'Much better'/ 'A little better'/ 'No change'.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[41]	309[42]		
Units: percentage of participants				
number (confidence interval 95%)	54.9 (48.05 to 61.58)	60.84 (55.3 to 66.12)		

Notes:

[41] - Treated Set (Only patients with observed cases (OC) values were analysed)

[42] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:	
Logistic regression with term treatment	
Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.1818
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.276
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.83

Notes:

[43] - Nintedanib 150mg versus placebo

Secondary: Time to Death Over 52 Weeks

End point title	Time to Death Over 52 Weeks

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of patients who did or did not experienced death before or at 372 days after randomisation or last contact date (whichever occurs first) are reported.
Failure is the proportion of patients who died over 52 weeks (up to 372 days after randomisation).

End point type	Secondary

End point timeframe:

0-52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[44]	309[45]		
Units: percentage of participants				
number (not applicable)				
Failure	6.4	4.2		
Censored	93.6	95.8		

Notes:

[44] - Treated Set (Only patients with observed cases (OC) values were analysed)

[45] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is based on Cox´s regression model with terms for treatment, gender, age and height.

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.288
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.36

Notes:

[46] - Nintedanib 150mg versus Placebo.

Secondary: Time to Death Due to Respiratory Cause Over 52 Weeks (Adjudicated)

End point title	Time to Death Due to Respiratory Cause Over 52 Weeks (Adjudicated)

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not experienced death due to
respiratory causes before or at 372 days after randomisation or last contact date (whichever occurs first) are reported.
Failure is the the proportion of patients who died due to respiratory causes over 52 weeks (up to 372 days after randomisation).

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[47]	309[48]		
Units: percentage of participants				
number (not applicable)				
Failure	4.9	3.2		
Censored	95.1	96.8		

Notes:

[47] - Treated Set (Only patients with observed cases (OC) values were analysed)

[48] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is based on Cox´s regression model with terms for treatment, gender, age and height

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.3515
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	1.47

Notes:

[49] - Nintedanib 150mg versus placebo

Secondary: Time to On-treatment Death

End point title	Time to On-treatment Death

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not die before or at last trial
medication intake + 28 days were censored at last trial medication intake + 28 days and reported. Failure is the the proportion of patients who died on-treatment (up to 28 days after last treatment intake).

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[50]	309[51]		
Units: percentage of participants				
number (not applicable)				
Failure	4.4	2.6		
Censored	95.6	97.4		

Notes:

[50] - Treated Set (Only patients with observed cases (OC) values were analysed)

[51] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is based on a Cox´s regression model with terms for treatment, gender, age and height

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.4869
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.82

Notes:

[52] - Nintedanib 150mg versus placebo

Secondary: Time to Death or Lung Transplant Over 52 Weeks

End point title	Time to Death or Lung Transplant Over 52 Weeks

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not experience event (death or lung transplant) before or at 372 days after randomisation or last contact date (whichever occurs first) are reported.
Failure is the proportion of patients who died or had lung transplant over 52 weeks (up to 372 days after randomisation).

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[53]	309[54]		
Units: percentage of participants				
number (not applicable)				
Failure	6.9	5.2		
Censored	93.1	94.8		

Notes:

[53] - Treated Set (Only patients with observed cases (OC) values were analysed)

[54] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is based on Cox´s regression model with terms for treatment, gender, age and height

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.443
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.51

Notes:

[55] - Nintedanib 150mg versus placebo

Secondary: Time to Death or Lung Transplant or Qualifying for Lung Transplant Over 52 Weeks.

End point title	Time to Death or Lung Transplant or Qualifying for Lung Transplant Over 52 Weeks.

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of participants who did or did not experienced death or lung transplant or qualifying for lung transplant over 52 weeks are reported. A patient was considered qualifying for lung transplant by the investigator if he or she fulfilled the following criteria:
FVC <45% predicted or Carbon monoxide diffusion capacity (DL(CO)) <30% pred or Oxygen saturation on pulse oximetry (SpO2) <88% at rest, at sea level (to be adapted for other heights).
These criteria were evaluated by investigators judgement.
Failure is the proportion of patients who died or had lung transplant or qualified for lung transplant over 52 weeks (373 days time-period).

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[56]	309[57]		
Units: percentage of participants				
number (not applicable)				
Failure	18.1	14.9		
Censored	81.9	85.1		

Notes:

[56] - Treated Set (Only patients with observed cases (OC) values were analysed)

[57] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is based on Cox´s regression model with terms for treatment, gender, age and height

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.3558
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.25

Notes:

[58] - Nintedanib 150mg versus placebo

Secondary: Change From Baseline in SpO2 (Oxygen Saturation, Expressed in Percent) at Rest up Over 52 Weeks

End point title	Change From Baseline in SpO2 (Oxygen Saturation, Expressed in Percent) at Rest up Over 52 Weeks

End point description:

Means presented are the adjusted means. Adjusted mean is based on all analyzed patients in the model (not only patients with a change from baseline to week 52)

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[59]	299[60]		
Units: percent of oxygen saturation				
arithmetic mean (standard error)	-0.53 (± 0.15)	-0.24 (± 0.129)		

Notes:

[59] - Treated Set (Only patients with observed cases (OC) values were analysed)

[60] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline SpO2, baseline SpO2-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	498
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.1138
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.181

Notes:

[61] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Proportion of FVC Responders Using 10% Threshold at 52 Weeks

End point title	Proportion of FVC Responders Using 10% Threshold at 52 Weeks

End point description:

FVC responders using 10% threshold at 52 weeks, defined as patients with absolute decline in FVC% predicted no greater than 10% and with an FVC evaluation at 52 weeks.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[62]	309[63]		
Units: percentage of participants				
number (confidence interval 95%)	56.86 (50 to 63.47)	70.55 (65.24 to 75.36)		

Notes:

[62] - Treated Set (Only patients with observed cases (OC) values were analysed)

[63] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Logistic regression with terms treatment, age, gender, height and baseline FVC % predicted

Comparison groups	Placebo v Nintedanib 150mg

Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.0007
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.914
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	2.79

Notes:

[64] - Nintedanib 150 mg bid versus Placebo

Secondary: Proportion of FVC Responders Using 5% Threshold at 52 Weeks

End point title	Proportion of FVC Responders Using 5% Threshold at 52 Weeks

End point description:

Proportion of FVC responders using 5% threshold at 52 weeks, defined as patients with absolute decline in FVC% predicted no greater than 5% and with an FVC evaluation at 52 weeks.

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[65]	309[66]		
Units: percentage of participants				
number (confidence interval 95%)	38.24 (31.84 to 45.06)	52.75 (47.18 to 58.25)		

Notes:

[65] - Treated Set (Only patients with observed cases (OC) values were analysed)

[66] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Logistic regression with terms treatment, age, gender, height and baseline FVC % predicted

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.847

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	2.66

Notes:

[67] - Nintedanib 150 mg bid versus Placebo

Secondary: Change From Baseline in EuroQol 5-Dimensional Quality of Life Questionnaire (EQ-5D) Health State up to 52 Weeks: Patient Reported Outcomes (PROs)

End point title	Change From Baseline in EuroQol 5-Dimensional Quality of Life Questionnaire (EQ-5D) Health State up to 52 Weeks: Patient Reported Outcomes (PROs)

End point description:

The EuroQol 5-dimensional Health State is based on a visual analog scale (EQ-VAS) representing the general patient's health state labelled from 100 (best imaginable health state) to 0 (worst imaginable health state). A higher score indicating a better health state. Change from baseline is calculated as the difference between health state at week 12, 24 and 52 respectively and health state at baseline as measured by the scale.

End point type	Secondary

End point timeframe:

baseline, 12 weeks, 24 weeks and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[68]	306[69]		
Units: points on a scale				
arithmetic mean (standard deviation)				
12 weeks (N= 194, 287)	0.04 (± 15.46)	-1.75 (± 16.42)		
24 weeks (N= 190, 279)	-0.84 (± 15.37)	-0.74 (± 17.92)		
52 weeks (N=160, 247)	-5.88 (± 19.17)	-2.46 (± 18.92)		

Notes:

[68] - Treated Set (Only patients with observed cases (OC) values were analysed)

[69] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Carbon Monoxide Diffusion Capacity (DLCO) at Rest Over 52 Weeks

End point title	Change From Baseline in Carbon Monoxide Diffusion Capacity (DLCO) at Rest Over 52 Weeks

End point description:

Means presented are the adjusted means. Adjusted mean is based on all analyzed patients in the model (not only patients with a change from baseline to week 52)

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[70]	286[71]		
Units: mmol/min/kPa				
arithmetic mean (standard error)	-0.365 (± 0.075)	-0.38 (± 0.0644)		

Notes:

[70] - Treated Set (Only patients with observed cases (OC) values were analysed)

[71] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed Model for Repeated Measures with fixed effects for treatment, visit, gender, age, height treatment-by-visit, baseline DLCO (HGB Corrected) [mmol/min/kPa], baseline DLCO (HGB Corrected) [mmol/min/kPa]-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.865
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.191
upper limit	0.161
Variability estimate	Standard error of the mean
Dispersion value	0.0896

Notes:

[72] - Nintedanib 150mg versus placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Time to First Acute Idiopathic Pulmonary Fibrosis (IPF) Exacerbation

End point title	Time to First Acute Idiopathic Pulmonary Fibrosis (IPF) Exacerbation

End point description:

Due to rare events, the median of time to event is not calculable, thus the percentages of patients with (IPF) exacerbation are reported and
represented as a key secondary endpoint.
An acute exacerbation (reported as an AE by the investigator) was defined as follows:
Otherwise unexplained clinical features including all of the following:
- Unexplained worsening or development of dyspnoea within 30 days
- New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the last visit
- Exclusion of infection as per routine clinical practice and microbiological studies

- Exclusion of alternative causes as per routine clinical practice including left heart failure, pulmonary embolism and identifiable cause of acute lung injury.

Failure is the proportion of patients with at least one acute IPF exacerbation over 52 weeks (up to randomisation + 372 days), based on all investigato

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[73]	309[74]		
Units: percentage of participants				
number (not applicable)				
Failure	5.4	6.1		
Censored	94.6	93.9		

Notes:

[73] - Treated Set (Only patients with observed cases (OC) values were analysed)

[74] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard Ratio is based on a Cox´s regression model with terms for treatment, gender, age and height

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[75]
P-value	= 0.6728
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.42

Notes:

[75] - Nintedanib 150 mg bid versus Placebo

Secondary: Relative Change From Baseline in FVC Over 52 weeks

End point title	Relative Change From Baseline in FVC Over 52 weeks

End point description:

Percentage change from baseline in FVC over 52 weeks. Means provided are the adjusted means and are based on all analysed patients in the model (not only patients with a change from baseline to week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[76]	307[77]		
Units: percent change				
arithmetic mean (standard error)	-7.38 (± 0.633)	-3.36 (± 0.55)		

Notes:

[76] - TS (Only patients with observed cases (OC) values were analysed)

[77] - TS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC, baseline FVC-by visit and random effect for patient.

Comparison groups	Nintedanib 150mg v Placebo
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.54
upper limit	5.5
Variability estimate	Standard error of the mean
Dispersion value	0.753

Notes:

[78] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Relative Change From Baseline in FVC (% predicted) over 52 weeks

End point title	Relative Change From Baseline in FVC (% predicted) over 52 weeks

End point description:

Percentage change from baseline in FVC (% predicted) at 52 weeks. Means provided are the adjusted means and are based on all analysed patients in the model (not only patients with a change from baseline to week 52).

End point type	Secondary

End point timeframe:

Baseline and 52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[79]	307[80]		
Units: percent change				
arithmetic mean (standard error)	-7.32 (± 0.634)	-3.32 (± 0.547)		

Notes:

[79] - TS (Only patients with observed cases (OC) values were analysed)

[80] - TS (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Based on Mixed Model for Repeated Measures (MMRM), with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC [%predicted], baseline FVC [%predicted]-by-visit and random effect for patient.

Comparison groups	Placebo v Nintedanib 150mg
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.52
upper limit	5.48
Variability estimate	Standard error of the mean
Dispersion value	0.753

Notes:

[81] - Nintedanib 150 mg bid versus Placebo.

Within-patient errors are modelled by compound symmetry covariance matrix.

Secondary: Risk of an Acute IPF Exacerbation Over 52 Weeks

End point title	Risk of an Acute IPF Exacerbation Over 52 Weeks

End point description:

Incidence rate of exacerbations (calculated as the number of patients with at least 1 acute IPF exacerbation divided by the total number of years at risk *100)

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo	Nintedanib 150mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[82]	309[83]		
Units: participants/Year*100				
number (not applicable)	5.6	6.6		

Notes:

[82] - Treated Set (Only patients with observed cases (OC) values were analysed)

[83] - Treated Set (Only patients with observed cases (OC) values were analysed)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk ratio was calculated as the ratio of risk of exacerbation in both treatment groups. The log of the risk ratio was assumed to follow a normal distribution with mean 0 and variance equal to the sum of the reciprocals of the number of patients with at least one exacerbation in each treatment arm.

Comparison groups	Nintedanib 150mg v Placebo
Number of subjects included in analysis	513
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.6793
Method	Normal distribution
Parameter estimate	Risk ratio (RR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.46

Notes:

[84] - Nintedanib 150mg bid versus placebo

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration, up to 425 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Oral administration of placebo matching nintedanib soft gelatine capsules.

Reporting group title	Nintedanib 150mg bid

Reporting group description:

Oral administration of soft gelatine capsules of Nintedanib 150 mg twice daily (bid). Dose interruption and reduction to 100 mg bid dose were allowed to manage adverse events.

Serious adverse events	Placebo	Nintedanib 150mg bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 204 (26.96%)	96 / 309 (31.07%)	
number of deaths (all causes)	14	19	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma			
subjects affected / exposed	3 / 204 (1.47%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			

subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 204 (0.00%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Metastases to liver			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	4 / 204 (1.96%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 204 (0.49%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microscopic polyangiitis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest discomfort			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 204 (0.98%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyp			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			

subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 204 (0.98%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 204 (1.47%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	11 / 204 (5.39%)	20 / 309 (6.47%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 4	0 / 7	

Pleurisy			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (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	1 / 204 (0.49%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 204 (1.47%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 204 (0.00%)	2 / 309 (0.65%)	
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	3 / 204 (1.47%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	6 / 204 (2.94%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 204 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 204 (1.47%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 204 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 204 (0.49%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

Atrial flutter			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomegaly			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	3 / 204 (1.47%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diastolic dysfunction			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 204 (0.49%)	4 / 309 (1.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			

subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 204 (0.98%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dysphagia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileus			
subjects affected / exposed	0 / 204 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (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 / 204 (0.00%)	1 / 309 (0.32%)	
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 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			

subjects affected / exposed	1 / 204 (0.49%)	3 / 309 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vasculitis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
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	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatic disorder			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			

subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 204 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 204 (0.98%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (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	3 / 204 (1.47%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 204 (0.00%)	2 / 309 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterial infection			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 204 (2.45%)	5 / 309 (1.62%)	
occurrences causally related to treatment / all	1 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
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	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 204 (0.49%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Viral infection			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 204 (0.49%)	0 / 309 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 204 (0.00%)	1 / 309 (0.32%)	
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	Placebo	Nintedanib 150mg bid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 204 (68.63%)	262 / 309 (84.79%)	
Investigations			
Weight decreased			
subjects affected / exposed	12 / 204 (5.88%)	24 / 309 (7.77%)	
occurrences (all)	12	25	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 204 (5.88%)	21 / 309 (6.80%)	
occurrences (all)	15	23	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	13 / 204 (6.37%)	14 / 309 (4.53%)	
occurrences (all)	14	17	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 204 (0.98%)	26 / 309 (8.41%)	
occurrences (all)	2	31	
Abdominal pain upper			
subjects affected / exposed	9 / 204 (4.41%)	23 / 309 (7.44%)	
occurrences (all)	11	28	
Constipation			
subjects affected / exposed	6 / 204 (2.94%)	17 / 309 (5.50%)	
occurrences (all)	6	18	
Diarrhoea			
subjects affected / exposed	38 / 204 (18.63%)	188 / 309 (60.84%)	
occurrences (all)	50	333	
Flatulence			
subjects affected / exposed	1 / 204 (0.49%)	18 / 309 (5.83%)	
occurrences (all)	1	19	
Nausea			
subjects affected / exposed	12 / 204 (5.88%)	70 / 309 (22.65%)	
occurrences (all)	13	94	
Vomiting			
subjects affected / exposed	4 / 204 (1.96%)	39 / 309 (12.62%)	
occurrences (all)	4	52	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 204 (12.75%)	47 / 309 (15.21%)	
occurrences (all)	30	51	
Dyspnoea			
subjects affected / exposed	21 / 204 (10.29%)	22 / 309 (7.12%)	
occurrences (all)	23	22	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	11 / 204 (5.39%)	10 / 309 (3.24%)	
occurrences (all)	11	10	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 204 (2.94%)	16 / 309 (5.18%)	
occurrences (all)	6	16	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 204 (7.84%)	17 / 309 (5.50%)	
occurrences (all)	17	19	
Infections and infestations			
Bronchitis			
subjects affected / exposed	27 / 204 (13.24%)	35 / 309 (11.33%)	
occurrences (all)	35	47	
Lower respiratory tract infection			
subjects affected / exposed	11 / 204 (5.39%)	16 / 309 (5.18%)	
occurrences (all)	14	32	
Nasopharyngitis			
subjects affected / exposed	34 / 204 (16.67%)	39 / 309 (12.62%)	
occurrences (all)	47	54	
Upper respiratory tract infection			
subjects affected / exposed	18 / 204 (8.82%)	28 / 309 (9.06%)	
occurrences (all)	23	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 204 (6.86%)	26 / 309 (8.41%)	
occurrences (all)	15	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2011	- 'Acute IPF exacerbation' was clarified each time 'exacerbation' was mentioned - Procedures and appropriate measures in case of suspicion of a 'drug induced liver injury' event were implemented - A re-test was allowed in case a laboratory parameter was found to be abnormal at Visit 1. This was to be conducted if laboratory tests were thought to be a measurement error and not related to the patient's condition - Patients were to be excluded from the trial if they were not able to follow trial procedures including completion of self administered questionnaires without help - Instructions were included for Investigators on the reporting of DLCO in the eCRF - Addition of the 'always serious AEs' according to new BI standards to ensure proper reporting of these events - Inclusion criterion 4 was changed to: 'Chest HRCT performed within 12 months of Visit 1', instead of 'Chest HRCT performed within 12 months of Visit 2'
04 September 2012	- Addition of exploratory biomarker analyses in order to explore the effect of nintedanib on biomarkers related to IPF pathology and prognostic markers of the disease. Exploratory analyses of samples from patients who gave specific informed consent were performed. Pharmacogenomic analysis was also added - The criterion for poor compliance was defined as a protocol violation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported