Clinical trial results:
A 12-week, double-blind, randomised, placebo-controlled, parallel-group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment

Summary

EudraCT number	2015-003148-38
Trial protocol	ES CZ FI HU GB BE FR DE PL
Global end of trial date	08 June 2018

Results information

Result version number	v1 (current)
This version publication date	15 June 2019
First version publication date	15 June 2019

Trial information

Trial identification

Sponsor protocol code	1199.227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02788474
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	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, 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	23 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2017
Global end of trial reached?	Yes
Global end of trial date	08 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial was conducted to examine for the first time the effects of nintedanib on the biomarkers indicative of ECM turnover to predict IPF progression. This trial also aimed to confirm the association between the change in these biomarkers during the first 12 weeks and disease progression over 52 weeks, and to assess whether nintedanib treatment could alter this association or not.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 21
Country: Number of subjects enrolled	Finland: 25
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Japan: 70
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 60
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	471
EEA total number of subjects	297

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)	98
From 65 to 84 years	365
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The trial comprised of 2 treatment periods (52 weeks). The first treatment period was a 12-week, randomised, double-blind, placebo-controlled, parallel-group period whereas the second treatment period was a 40-week, single-arm, open-label, active treatment (nintedanib 150 milligram (mg) twice daily (bid)) period.

Pre-assignment

Screening details:

Participants with idiopathic pulmonary fibrosis (IPF) were eligible for trial if they fulfilled all of the inclusion criteria and none of the exclusion criteria. Subjects attended specialist sites to ensure that they met all implemented inclusion/exclusion criteria and were not to be randomized to drug if any of the specific criteria was violated.

Period 1

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

Blinding implementation details:

Patients, investigators and everyone involved in the trial conduct or analysis or with any other interest in this trial remained blinded with regard to randomised treatment assignments until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Nintedanib

Arm description:

Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period and Nintedanib 150 milligram (mg) twice daily (bid) for 40 weeks in open label period. 1 capsule of Nintedanib 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs).
1 patient was randomised to the this arm, however this patient was not treated.
Consequently, number of subjects that started is 231 but only 230 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:

Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period

Arm title	Nintedanib/Nintedanib

Arm description:

Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)

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:

Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period

Number of subjects in period 1[1]	Placebo/Nintedanib	Nintedanib/Nintedanib
Started	230	116
Completed	221	112
Not completed	9	4
Patient's refusal	3	-
Adverse event, non-fatal	6	4

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

Period 2

Period 2 title	Open label treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The period was a 40-week, single arm, open-label, active treatment period during which all patients received nintedanib 150 mg bid

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/Nintedanib

Arm description:

Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period and Nintedanib 150 milligram (mg) twice daily (bid) for 40 weeks in open label period. 1 capsule of Nintedanib 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)

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

Dosage and administration details:

Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period.

Arm title	Nintedanib/Nintedanib

Arm description:

Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)

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:

Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)

Number of subjects in period 2	Placebo/Nintedanib	Nintedanib/Nintedanib
Started	221	112
Completed	189	100
Not completed	32	12
Patient's refusal	1	3
Adverse event, serious fatal	4	3
Other than reason specified	1	-
Adverse event, non-fatal	25	6
Non-compliance	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/Nintedanib
Reporting group description:	
Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period and Nintedanib 150 milligram (mg) twice daily (bid) for 40 weeks in open label period. 1 capsule of Nintedanib 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs). 1 patient was randomised to the this arm, however this patient was not treated. Consequently, number of subjects that started is 231 but only 230 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.	
Reporting group title	Nintedanib/Nintedanib
Reporting group description:	
Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)	

Reporting group values	Placebo/Nintedanib	Nintedanib/Nintedanib	Total
Number of subjects	230	116	346
Age categorical Units: Subjects			
Age Continuous			
Treated Set (TS), consisting of participants who were randomised to a treatment group and received at least one dose of trial medication			
Units: years			
arithmetic mean	70.2	70.5	
standard deviation	± 7.2	± 7.7	-
Sex: Female, Male			
Treated Set (TS), consisting of participants who were randomised to a treatment group and received at least one dose of trial medication			
Units: Subjects			
Female	61	23	84
Male	169	93	262
Race (NIH/OMB)			
Unreported data: Data not collected at sites in France due to local regulation. Treated Set (TS), consisting of participants who were randomised to a treatment group and received at least one dose of trial medication			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	68	35	103
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	144	70	214
More than one race	0	0	0
Unknown or Not Reported	18	11	29
Ethnicity (NIH/OMB)			
Unreported data: Data not collected at sites in France due to local regulation. Treated Set (TS), consisting of participants who were randomised to a treatment group and received at least one dose of trial medication			
Units: Subjects			

Hispanic or Latino	19	9	28
Not Hispanic or Latino	193	96	289
Unknown or Not Reported	18	11	29

End points

End points reporting groups

Reporting group title	Placebo/Nintedanib
Reporting group description:	
Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period and Nintedanib 150 milligram (mg) twice daily (bid) for 40 weeks in open label period. 1 capsule of Nintedanib 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs). 1 patient was randomised to the this arm, however this patient was not treated. Consequently, number of subjects that started is 231 but only 230 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.	
Reporting group title	Nintedanib/Nintedanib
Reporting group description:	
Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)	
Reporting group title	Placebo/Nintedanib
Reporting group description:	
Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period and Nintedanib 150 milligram (mg) twice daily (bid) for 40 weeks in open label period. 1 capsule of Nintedanib 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)	
Reporting group title	Nintedanib/Nintedanib
Reporting group description:	
Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)	

Primary: The rate of change (slope) in blood C-reactive protein degraded by matrix metalloproteinase-1/8 (CRPM) from baseline to week 12.

End point title	The rate of change (slope) in blood C-reactive protein degraded by matrix metalloproteinase-1/8 (CRPM) from baseline to week 12.
End point description:	
The rate of change (slope) in blood C-reactive protein degraded by matrix metalloproteinase-1/8 (CRPM) from baseline to week 12 is presented. The mean presented is the adjusted rate based on a random coefficient regression (CRPM log 10 transformed) with fixed effects for gender, age, height and random effect of patient specific intercept and time.	
End point type	Primary
End point timeframe:	
baseline and 12 weeks	

End point values	Placebo/Nintedanib	Nintedanib/Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229[1]	116[2]		
Units: nanogram/ millitre/ month (ng/ mL/ mth)				
arithmetic mean (standard error)	-0.00190 (± 0.00165)	-0.00257 (± 0.00232)		

Notes:

[1] - TS including participants with available data for this endpoint.

[2] - TS including participants with available data for this endpoint.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The rate of change (slope) in blood CRPM was assumed to be linear in each subject over the 12 weeks of treatment. The intercepts and slopes were assumed to be normally distributed with arbitrary covariance matrix. Since the distribution of the data was not normal, a log10 transformation was performed before conducting the statistical analyses. Significance tests were based on least-square means using 2-sided 95% confidence intervals (2-sided α=0.05).

Comparison groups	Placebo/Nintedanib v Nintedanib/Nintedanib
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.8146 [4]
Method	random coefficient regression
Parameter estimate	Adjusted mean difference
Point estimate	-0.00066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.00621
upper limit	0.00488
Variability estimate	Standard error of the mean
Dispersion value	0.00282

Notes:

[3] - The Kenward-Roger approximation was used to estimate denominators degrees of freedom. Difference calculated as Nintedanib minus Placebo

[4] - random coefficient regression (random slopes and intercepts) model including sex, age and height as covariates (Due to the low number of measurements per patient, baseline CRPM was included as a response rather than as a covariate in the analysis)

Secondary: Percentage of patients with disease progression as defined by absolute forced vital capacity (FVC) decline >=10% or death until week 52

End point title	Percentage of patients with disease progression as defined by absolute forced vital capacity (FVC) decline >=10% or death until week 52

End point description:

For this endpoint, disease progression was defined by absolute FVC (percentage of predicted) decline ≥10% or death up to Week 52 based on in-clinic supervised spirometry. CRPM was also log 10 transformed for this key secondary endpoint.

Within group (for Placebo/Nintedanib) statistical analysis (Statistical analysis 1) for present outcome measure was defined and analysed in the clinical trial report (To assess the association between the change in the Extracellular matrix (ECM) biomarker CRPM in the first 12 weeks and disease progression over 52 weeks, a logistic regression analysis including baseline blood CRPM and the monthly rate of change (slope) in blood CRPM in the first 12 weeks as covariates was applied for placebo-treated patients only to evaluate the potential of CRPM as a prognostic biomarker). However, due to the platform limitation those could not be disclosed on EudraCT, but can be found on ct.gov under study number: NCT02788474

End point type	Secondary

End point timeframe:

52 weeks

End point values	Placebo/Nintedanib	Nintedanib/Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[5]	116[6]		
Units: Percentage of participants				
number (confidence interval 95%)	30.43 (24.85 to 36.66)	25.00 (18.01 to 33.60)		

Notes:

[5] - TS

[6] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

To assess how nintedanib treatment affected the association between the change in CRPM in the first 12 weeks and disease progression over 52 weeks, a logistic regression analysis including baseline blood CRPM, the monthly rate of change (slope) in blood CRPM up to Week 12, treatment and treatment-CRPM slope interaction as covariates was applied.

Comparison groups	Placebo/Nintedanib v Nintedanib/Nintedanib
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1537
Method	Regression, Logistic
Parameter estimate	slope estimate
Point estimate	-45.566
Confidence interval	
level	95 %
sides	2-sided
lower limit	-109.55
upper limit	16.37

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

To assess whether the overall treatment regimen affected disease progression, a logistic regression analysis including baseline blood CRPM and randomised treatment as covariates was applied.

Comparison groups	Placebo/Nintedanib v Nintedanib/Nintedanib
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3116
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.769

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.27

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

To assess whether the monthly rate of change (slope) in blood CRPM in the first 12 weeks could explain the effect of treatment on disease progression, a logistic regression analysis including baseline blood CRPM, the rate of change (slope) in blood CRPM in the first 12 weeks and randomised treatment as covariates was applied.

Comparison groups	Placebo/Nintedanib v Nintedanib/Nintedanib
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3175
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.772
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.27

Secondary: The rate of change in blood Collagen 1 degraded by matrix metalloproteinase-2/9/13 (C1M) from baseline to week 12

End point title	The rate of change in blood Collagen 1 degraded by matrix metalloproteinase-2/9/13 (C1M) from baseline to week 12

End point description:

The rate of change in blood Collagen 1 degraded by matrix metalloproteinase-2/9/13 (C1M) from baseline to week 12 is presented. The mean presented is the adjusted rate based on a random coefficient regression (C1M (negative reciprocal root transformation)) with fixed effects for gender, age, height and random effect of patient specific intercept and time.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Placebo/Nintedanib	Nintedanib/Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229[7]	116[8]		
Units: ng/ml/mth				
arithmetic mean (standard error)	0.00041 (± 0.00127)	0.00162 (± 0.00172)		

Notes:

[7] - Treated set (TS) including participants with available data for this endpoint.

[8] - Treated set (TS) including participants with available data for this endpoint.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The rate of change (slope) in blood C1M was assumed to be linear in each subject over the 12 weeks of treatment. Within−patient errors are modelled by an Unstructured variance−covariance matrix.

Comparison groups	Placebo/Nintedanib v Nintedanib/Nintedanib
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.5469 [10]
Method	random coefficient regression
Parameter estimate	Adjusted mean difference
Point estimate	0.00121
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.00273
upper limit	0.00515
Variability estimate	Standard error of the mean
Dispersion value	0.002

Notes:

[9] - Difference calculated as Nintedanib minus Placebo. Inter−individual variability is modelled by a Variance−Components variance−covariance
matrix.

[10] - random coefficient regression model (C1M (negative reciprocal root-transformed)) with fixed effects for gender, age, height and random effect of patient specific intercept and time.

Secondary: The rate of change in blood Collagen 3 degraded by matrix metalloproteinase-9 (C3M) from baseline to week 12

End point title	The rate of change in blood Collagen 3 degraded by matrix metalloproteinase-9 (C3M) from baseline to week 12

End point description:

The rate of change in blood Collagen 3 degraded by matrix metalloproteinase-9 (C3M) from baseline to week 12 is presented. The mean presented is the adjusted rate based on a random coefficient regression (C3M- log 10 transformation) with fixed effects for gender, age, height and random effect of patient specific intercept and time.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Placebo/Nintedanib	Nintedanib/Nintedanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229[11]	116[12]		
Units: ng/ml/mth				
arithmetic mean (standard error)	-0.00091 (± 0.00158)	-0.00398 (± 0.00219)		

Notes:

[11] - Treated set (TS) including participants with available data for this endpoint.

[12] - Treated set (TS) including participants with available data for this endpoint.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The rate of change (slope) in blood C3M was assumed to be linear in each subject over the 12 weeks of treatment. Within−patient errors are modelled by an Unstructured variance−covariance matrix.

Comparison groups	Placebo/Nintedanib v Nintedanib/Nintedanib
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.2429 [14]
Method	random coefficient regression
Parameter estimate	Adjusted mean difference
Point estimate	-0.00307
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.00823
upper limit	0.00209
Variability estimate	Standard error of the mean
Dispersion value	0.00262

Notes:

[13] - Difference calculated as Nintedanib minus Placebo. Inter−individual variability is modelled by a Variance−Components variance−covariance matrix.

[14] - random coefficient regression model (C3M (log10-transformed)) with fixed effects for gender, age, height and random effect of patient specific intercept and time.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE & Non SAE: Adverse events (AEs) that occurred between first drug intake and 28 days after last drug intake (end of the Residual effect period (REP));up to 53 weeks
All cause mortality: AEs during the course of the clinical trial;up to 56 weeks

Adverse event reporting additional description:

Treated set is used for reporting adverse events (Serious Adverse Event (SAE) & Non SAE)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo/Nintedanib

Reporting group description:

Participants received soft gelatin capsules of matching placebo for 12 weeks in double blind period and Nintedanib 150 milligram (mg) twice daily (bid) for 40 weeks in open label period. 1 capsule of Nintedanib 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs). 1 patient was randomised to the this arm, however this patient was not treated. Consequently, number of subjects that started is 231 but only 230 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Nintedanib/Nintedanib

Reporting group description:

Participants received soft gelatin capsules of Nintedanib 150 mg bid for 12 weeks in double blind period and for 40 weeks in open label period. 1 capsule of 150 mg bid had possibility to be reduced to 100 mg bid to manage adverse events (AEs)

Serious adverse events	Placebo/Nintedanib	Nintedanib/Nintedanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 230 (28.70%)	20 / 116 (17.24%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 230 (0.43%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	3 / 230 (1.30%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microscopic polyangiitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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			
Chest pain			
subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 230 (0.43%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Disease progression			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Incarcerated hernia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
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	1 / 230 (0.43%)	0 / 116 (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			
Dyspnoea			

subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	5 / 230 (2.17%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 230 (0.43%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 230 (0.43%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza B virus test positive			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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			
Ankle fracture			
subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 230 (0.87%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pulmonary arteriovenous fistula			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			

subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 230 (0.87%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden hearing loss			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	2 / 230 (0.87%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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	2 / 230 (0.87%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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			
Arthralgia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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			
Abdominal abscess			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendicitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 116 (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	1 / 230 (0.43%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 230 (0.43%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 230 (1.74%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 230 (1.74%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 116 (0.86%)	
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	Nintedanib/Nintedanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 230 (89.57%)	108 / 116 (93.10%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 230 (5.65%)	12 / 116 (10.34%)	
occurrences (all)	15	14	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 230 (6.09%)	10 / 116 (8.62%)	
occurrences (all)	17	10	
Gamma-glutamyltransferase increased			
subjects affected / exposed	16 / 230 (6.96%)	6 / 116 (5.17%)	
occurrences (all)	16	7	
Weight decreased			
subjects affected / exposed	22 / 230 (9.57%)	11 / 116 (9.48%)	
occurrences (all)	23	11	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 230 (3.91%)	7 / 116 (6.03%)	
occurrences (all)	13	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 230 (4.35%)	6 / 116 (5.17%)	
occurrences (all)	12	7	
Headache			
subjects affected / exposed	20 / 230 (8.70%)	9 / 116 (7.76%)	
occurrences (all)	26	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 230 (0.87%)	6 / 116 (5.17%)	
occurrences (all)	2	9	
Fatigue			

subjects affected / exposed	11 / 230 (4.78%)	6 / 116 (5.17%)	
occurrences (all)	11	6	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 230 (2.17%)	9 / 116 (7.76%)	
occurrences (all)	5	9	
Abdominal pain			
subjects affected / exposed	18 / 230 (7.83%)	9 / 116 (7.76%)	
occurrences (all)	22	15	
Abdominal pain upper			
subjects affected / exposed	19 / 230 (8.26%)	4 / 116 (3.45%)	
occurrences (all)	20	4	
Constipation			
subjects affected / exposed	10 / 230 (4.35%)	10 / 116 (8.62%)	
occurrences (all)	12	12	
Diarrhoea			
subjects affected / exposed	158 / 230 (68.70%)	92 / 116 (79.31%)	
occurrences (all)	366	214	
Dyspepsia			
subjects affected / exposed	8 / 230 (3.48%)	6 / 116 (5.17%)	
occurrences (all)	8	6	
Flatulence			
subjects affected / exposed	7 / 230 (3.04%)	6 / 116 (5.17%)	
occurrences (all)	8	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	13 / 230 (5.65%)	7 / 116 (6.03%)	
occurrences (all)	13	7	
Nausea			
subjects affected / exposed	55 / 230 (23.91%)	23 / 116 (19.83%)	
occurrences (all)	78	32	
Vomiting			
subjects affected / exposed	34 / 230 (14.78%)	18 / 116 (15.52%)	
occurrences (all)	58	34	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	37 / 230 (16.09%)	18 / 116 (15.52%)	
occurrences (all)	45	23	
Dyspnoea			
subjects affected / exposed	12 / 230 (5.22%)	6 / 116 (5.17%)	
occurrences (all)	18	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	23 / 230 (10.00%)	8 / 116 (6.90%)	
occurrences (all)	25	9	
Infections and infestations			
Bronchitis			
subjects affected / exposed	19 / 230 (8.26%)	11 / 116 (9.48%)	
occurrences (all)	24	16	
Influenza			
subjects affected / exposed	7 / 230 (3.04%)	6 / 116 (5.17%)	
occurrences (all)	9	6	
Lower respiratory tract infection			
subjects affected / exposed	13 / 230 (5.65%)	8 / 116 (6.90%)	
occurrences (all)	22	18	
Nasopharyngitis			
subjects affected / exposed	44 / 230 (19.13%)	25 / 116 (21.55%)	
occurrences (all)	56	31	
Respiratory tract infection			
subjects affected / exposed	12 / 230 (5.22%)	6 / 116 (5.17%)	
occurrences (all)	15	6	
Upper respiratory tract infection			
subjects affected / exposed	20 / 230 (8.70%)	9 / 116 (7.76%)	
occurrences (all)	29	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 230 (16.52%)	21 / 116 (18.10%)	
occurrences (all)	41	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2016	The document number was corrected on the title page and headers.
25 February 2016	No content changes were introduced. A technical error during signature workflow was corrected.
04 May 2017	The following main changes in the conduct of the trial and clarifications were introduced: - Serum, plasma, RNA, PK and optional serum banking sample collections were added to the flow chart - Fingertip was added as a possibility to perform measurements of oxygen saturation - Further explanations were added concerning visit planning and conduct The below amendment exists but was issued after the global end of the trial date: Amendment dated: 09Jul2018 The following main changes in the analysis of the data were implemented: - The analysis of the PFT data was detailed further by adding 4 endpoints: the proportion of patients with absolute FVC decline ≥10% until Week 52, the proportion of patients with absolute FVC decline ≥5% until Week 52, the time to FVC decline ≥10%, and the time to FVC decline ≥5% - The analysis of the LOXL2 specific cross-linking fragment was deleted because the analysis kit had not been validated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported